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ENDEAVOUR

The British quarterly scientific journal ENDEAVOUR was first published, by Imperial Chemical Industries Limited, in January 1942. Its purpose is to provide scientists, especially those overseas, with news of the progress of the sciences. While emphasis is laid upon British work, occasional articles from overseas contributors are included and impartial reference is made to the world's scientific literature. To make the journal truly international in character it is published in five separate editions—English, French, German, Italian, and Spanish.

No charge is made for ENDEAVOUR. It is distributed to senior scientists, scientific institutions, and libraries throughout the world, the guiding principle being that of helping scientists overseas to maintain those contacts which their British colleagues have always so much valued. Within these limits the Editors are at all times glad to consider the addition of new names to the mailing list.

The drawing on the cover is of the bark Endeavour, *which, commanded by Captain James Cook and carrying a number of scientific workers, was sent out by the British Admiralty in* 1768 *to chart the South Pacific Ocean and observe the transit of Venus*

ENDEAVOUR

A quarterly review, published in five languages,
designed to record the progress of the sciences
in the service of mankind

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Eric John Holmyard

With the death of E. J. Holmyard on 13th October 1959, ENDEAVOUR lost its first Editor and one whose original ideas are still firmly imprinted on the journal. It is a measure of his greatness that the general format and scientific policy of ENDEAVOUR have been changed relatively little since the first issue was published in 1942, when to all the other problems of planning and producing a new international review were added the severe practical difficulties arising from the war. But to begin a tribute to Holmyard with an account of his contribution to ENDEAVOUR is to anticipate events, for he had already established his name in a different sphere, as a teacher and historian of science.

He was born in Midsomer Norton, Somerset, in 1891 and was educated at Sexey's School, Bruton, and Sidney Sussex College, Cambridge. His first appointment after graduation was at Rothamsted Experimental Station, where he was for a year one of the Board of Agriculture's first Research Scholars, but he quickly decided that his true vocation was as a teacher. After brief appointments at Bristol Grammar School and Marlborough, he became Head of the Science Department at Clifton College, where he established a very successful school of science: he combined a deep love of science with a very clear understanding of the rigour of its discipline, and both of these he managed to inculcate in his students. In later life, nothing gave him greater pleasure than to learn of distinctions gained by his former pupils, all of whom owe much to his inspiring teaching. During this period he developed a deep interest in the history of science, especially of alchemy: to further this, he taught himself Arabic in order to be able to read original Islamic manuscripts. He was a great believer in the value of the historical approach in teaching, and this belief found expression in a number of very successful text-books of chemistry, written in a style different from any that had preceded them, of which several are still in use. Through these text-books he had a far-reaching influence on the teaching of science, not only in Britain but in all the Commonwealth countries. As an historian of science he quickly established an international reputation, and in 1928 his important contributions to scholarship were recognised by the award of the D.Litt. degree of the University of Bristol. He was chairman of the Society for the Study of Alchemy and Early Chemistry and *Membre Correspondant de l'Académie Internationale de l'Histoire des Sciences*. His 'Alchemy', published in 1957, was widely welcomed as a valuable addition to the literature of the subject.

Holmyard retired from Clifton in 1940, shortly before Imperial Chemical Industries conceived the idea of ENDEAVOUR as a new multilingual journal which would tell the story of Britain's contribution to the progress of science: that he was free to accept their invitation to become the first Editor was a major factor in the success of the new venture. In some ways this was a new departure for him, but in another it was a logical development of his earlier career —he continued to tell the story of science, but to an international readership. When the war ended, ENDEAVOUR had so firmly established its reputation under his guidance that it was decided to continue its publication indefinitely. Of the value of his work as Editor until his retirement in 1954 the volumes of ENDEAVOUR are eloquent testimony. He took great pride in the journal, with which he continued to be associated as an adviser until his death.

From 1950 onwards he made a further great contribution to international scholarship through the five-volume 'History of Technology'—the result of a collaboration between Imperial Chemical Industries and the Clarendon Press, Oxford—of which he was a joint editor. His great knowledge and meticulous attention to detail contributed much to the success of this massive work.

Despite his exceptional talents, Holmyard was of an unassuming and retiring disposition, and his influence on the world of learning was made far more through his extensive writings than through personal contact. But his friends knew him as a man of great charm, unfailingly helpful to those who sought his aid: their loss is indeed great.

The mast cells

J. F. RILEY

The mast cells, connective-tissue cells that are selectively stained by basic dyes, were first described by Ehrlich during the research that led to chemotherapy. The study of the natural anticoagulant, heparin, and that of histamine have, surprisingly, linked with the investigation of the mast cells. This investigation appears to be about to enter a new phase; the present state of research, and the possible lines of progress are described in this article.

Tissue mast cells were first clearly described by Paul Ehrlich (1854–1915) while still a medical student. Ehrlich, witnessing the introduction of differential staining of tissues for examination under the microscope, was drawn to consider the mechanism whereby selective staining occurs. His vivid imagination pictured an interlocking of molecules of complementary shape in dye and protoplasm. This, in turn, led to his studies on chemotherapy and to the tailoring of the organic arsenicals to fit the spirochaetes of syphilis.

Ehrlich's first attempt to demonstrate specific affinities was to study the effects on living tissues of the new aniline dyes then being synthesized by German chemists. In so doing he discovered that certain connective tissue cells contain cytoplasmic granules that stain selectively with basic dyes (figures 1 and 3). His belief that this represents a specific chemical reaction was strengthened by his observation that the colour of the dye changes as staining occurs: a blue dye, such as toluidine blue, turns purple to red; a red dye, such as neutral red, turns orange to yellow. Ehrlich named the change metachromasia. It was, in fact, the beginnings of a new branch of biology, histochemistry, though it was many years before the histochemical significance of metachromasia was discovered.

Ehrlich found few cells with metachromatic granules in the embryos of various species, though they are common in the adult forms, especially in loose, well-nourished, connective tissue. They occur in the skin, in the peritoneum, in the capsules of organs, and around structures which traverse the connective tissue—blood vessels, ducts, nerves. The granular cells were found to be so common in the connective tissue in chronic inflammation and where the cells are bathed in protein-rich lymph that Ehrlich named them *Mastzellen* (well-fed cells), using the prefix in the sense that hogs are fattened on beech 'mast.' Thus he regarded the mast cells as indices of the nutritional state of the connective tissues, and their granules as a reserve foodstuff. Much of what we know about mast cells was known to Ehrlich, whose graduation thesis has only very recently become available for study [1].

His final contribution to the story of the mast cells was his discovery of somewhat similar cells, also with basophilic metachromatic granules, in the blood. However, with characteristic insight, he at once perceived that the blood mast cells (basophils or mast leucocytes) are derived from the bone marrow, along with the eosinophils and polymorphs. Tissue mast cells, on the other hand, are born, live, and die in the connective tissues. With few exceptions, the numbers of mast cells in the blood are small in comparison with the abundance of such cells in the connective tissues.

THE MAST CELL AND HEPARIN

The next advance in our knowledge of the mast cells came sixty years later and from so unexpected a quarter that a brief consideration of the background is desirable before both the strength and the weakness of the work can be appreciated.

The mechanism whereby the blood remains fluid while circulating, and yet clots when it is shed, has excited speculation from the earliest times. At the beginning of the present century it was generally felt that the blood must contain an anticoagulant which is neutralized when clotting occurs. The discovery of an enzymatic mechanism and of the need for calcium ions in the clotting process, still left open the possibility that the body normally produces its own anticoagulant. In 1916 Jay McLean, in Howell's laboratory in Baltimore, isolated from the liver of a dog what appeared at first to be a phosphatide with the properties of a powerful anticoagulant. In recognition of its origin the new substance was named heparin. Haematologists eagerly incorporated heparin into the clotting equations and continued to retain the

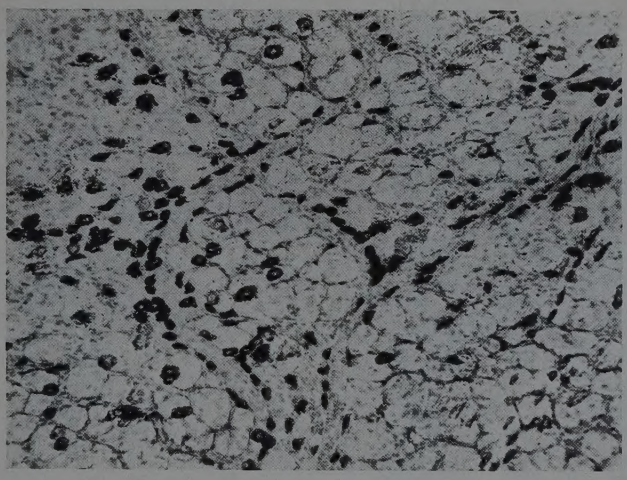


FIGURE 1 – *Tissue spread of rat subcutaneous connective tissue. The dark spots (some of which show a clear nuclear space in the centre) are the mast cells. These commonly arise near blood vessels but thereafter tend to move away and mature in the nearby connective tissue. (Toluidine blue,* × 90)

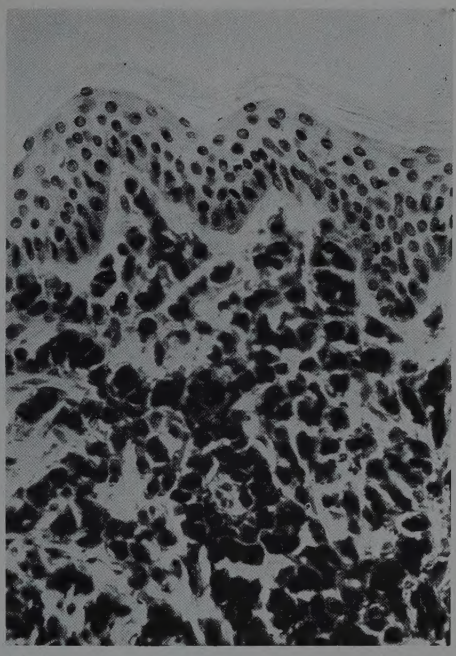


FIGURE 2 – *Vertical paraffin section through the skin of a child with urticaria pigmentosa. Under the epidermis (whose nuclei have been lightly counter-stained) are numerous dark mast cells. Injury to an area showing urticaria pigmentosa is followed by a release of histamine from the mast cells. (Toluidine blue–haemalum,* × 300)

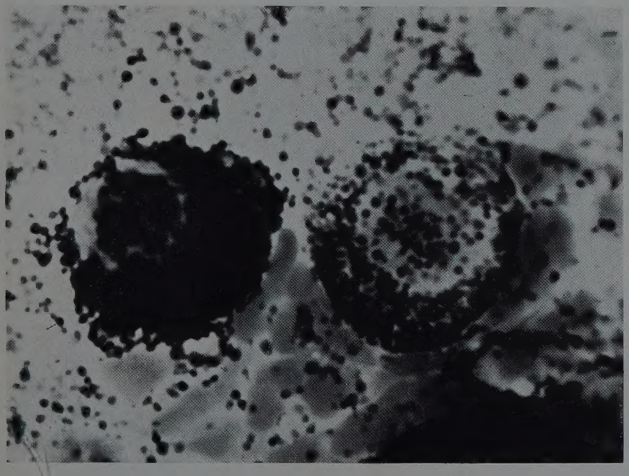
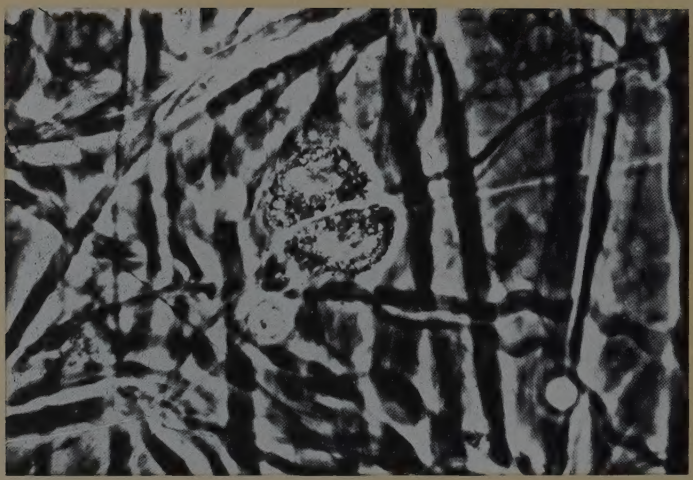
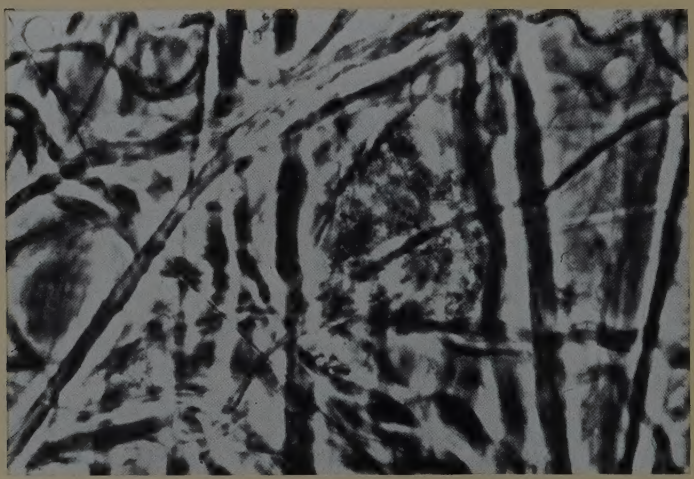


FIGURE 3 (*left*) – *Rapid diagnosis of a mast-cell tumour from a mouse. An imprint from a cut surface of the tumour is made on a microscope slide. Some of the cells adhere to the glass and can be stained as in a blood film. Of the two cells in the photograph, one is well filled, and the other is partly filled, with characteristic metachromatic granules. Scattered granules lie around the cells. (Leishman-Giemsa stain,* × 1500)

name even when it was discovered that heparin occurs widely in the body and not only in the liver. Scandinavian chemists, led by J. E. Jorpes of Stockholm [2], then showed that heparin is not a phosphatide, as was originally thought, but an acid mucopolysaccharide, a polymer of disaccharide units of glucuronic acid and glucosamine, extensively esterified with sulphate. Meanwhile Lison, in Belgium, had concluded that metachromasia in tissue sections is acceptable evidence of the presence of a polysulphuric acid ester of high molecular weight. With these two pieces of information available, it remained merely to correlate heparin yield with some recognizable metachromatic component in the tissues to determine the site of formation or storage of heparin in the body.

It had long been known that normal articular cartilage and the pathological material, amyloid, stain metachromatically with toluidine blue. Neither, however, yields an anticoagulant on extraction. On the other hand, an excellent correlation was found between mast-cell content and heparin yield. The hypothesis that the metachromatic substance of the mast-cell granule is heparin received overwhelming support when it was discovered that a small mast-cell tumour in the skin of a dog can yield, on extraction, more heparin than the dog's whole liver, the organ from





FIGURES 4, 5, and 6 – *These three photographs, taken by phase-contrast microscopy, show in sequence the explosive effects on living mast cells of a chemical histamine-liberator. A rat is anaesthetized and a loop of intestine is draped over the microscope stage and irrigated with Ringer-Locke solution. Figure* 4 *shows a pair of well granulated mast cells lying among wavy connective-tissue fibrils of the peritoneum. Compound* 48/80 *(a specific histamine-liberator for the rat) is then run on to the preparation. The mast cells promptly undergo swelling, degranulation, and disruption, as shown in figures* 5 *and* 6. (×1200)

which heparin received its name. Very recently, mast cells have been harvested from the peritoneal cavity of rats in quantities sufficient for analysis. As Jorpes remarks: 'There is no doubt whatsoever about the nature of the granular substance of the mast cells. It is heparin'.

The chemical evidence for heparin in mast cells is thus entirely convincing; it is the biological significance of heparin in the organism that is still not settled. Nevertheless, the new work did appear to offer a plausible explanation for the common perivascular distribution of the mast cells. It was assumed that the mast cell produces heparin, an anticoagulant, which is then discharged through the vessel wall into the blood stream to prevent clotting. For a while, at least, it seemed that what Ehrlich had called the 'riddle of the mast cell' had been solved. Looking at the situation in retrospect we see that much of the alleged significance of the mast cell as a 'heparinocyte' was thrust upon it by haematologists who saw in the new work support for current views on blood clotting. The views of Ehrlich and the early histologists were temporarily forgotten.

THE MAST CELL AND HISTAMINE

Histamine is one of a group of naturally occurring basic amines having pharmacological actions on plain muscle and on the permeability of small blood vessels. The work of Sir Thomas Lewis and Sir Henry Dale had shown that a local injection of histamine can reproduce exactly the classical reaction of the skin to injury, the so-called 'triple response'. Other workers found reason to suspect that histamine is causally involved in allergy and in anaphylaxis (specific supersensitiveness to a second dose of a foreign protein) in certain species. However, the precise cytological location of histamine remained unknown.

The fiftieth anniversary of the discovery of anaphylaxis by Portier and Richet was celebrated in 1952. Three years later, physiologists and pharmacologists were preparing to hold a joint symposium on histamine in honour of the eightieth birthday of Sir Henry Dale. There was thus that desirable element of timeliness in reports published in 1954, near the centenary of the birth of Ehrlich, that the mast cells contain not only heparin but also the bulk of the histamine in the body [3, 4].

Two main considerations led to the hypothesis that the tissue mast cell is rich in histamine. The first is that either an injection of peptone into a normal dog, or a second injection of a foreign protein into a dog made sensitive to that protein, is followed by a syndrome of shock in which the liver of the dog swells, its blood pressure falls, and the circulating blood becomes incoagulable. The shock is a histamine shock; the cause of the prolonged clotting time is a release of heparin into the blood. Heparin comes from the mast cells, of which there are many in the liver of the dog. Could it be that both the histamine and the heparin are derived from the same source—even from the same cell?

The second consideration turned upon the exaggerated 'triple response' which can be provoked in the skin of the human subject with urticaria pigmentosa, a skin disease characterized histologically by an abundance of mast cells (figure 2).

As with heparin on a former occasion, it was now shown that mast-cell tumours in dogs, and the lesions of urticaria pigmentosa in man, are outstandingly rich in histamine. Indeed, it seems that both heparin and histamine can be manufactured enzymatically in the granules of the mast cell. The tissue mast cells of the mouse (figure 3) and rat are curious in that they contain, in addition to histamine, small amounts of a second amine: this is 5-hydroxytryptamine (serotonin) which occurs mainly in the enterochromaffin cells of the gut [5].

Thus we see that one hundred years after the birth of Ehrlich, the mast cells which he believed to be food cells of the connective tissue had been shown to contain first, a powerful anticoagulant, heparin, and second, one amine or more capable of acting on plain muscle and on the permeability of small blood vessels. Both heparin and histamine manifest their actions in certain pathological states. Can we say that either action points to the physiological function of the mast cell in the normal organism?

THE CHEMICAL HISTAMINE-LIBERATORS

A powerful stimulus to a direct experimental investigation of the cytological location of tissue histamine was the discovery of the chemical histamine-liberators, a somewhat heterogeneous group of compounds whose common property is to release histamine from its depots in the tissues [6].

Some of the histamine-liberators fluoresce in ultra-violet light. When such liberators are traced to their targets in the tissues of a rat, it is seen that they first become concentrated in the mast cells of the peritoneum, which then undergo a series of changes—swelling, degranulation, disruption—which are accompanied by a fall in assayable histamine (figures 4–6) [14].

It is doubtful whether such a release of histamine from its main depots in the tissues by the chemical histamine-liberators corresponds closely to the release of histamine in anaphylaxis. For example, the skin of a rat can be virtually cleared of its histamine and yet give an unimpaired anaphylactic response [7]: indeed, the most recent evidence suggests that neither the mast cell nor histamine is concerned in the anaphylactic reaction in the rat [8]. However, the study of anaphylaxis provides ample evidence of the errors to be met with when data from one species are uncritically transferred to another. The reader is referred to the wise words of Sir Henry Dale, written for the Portier-Richet celebrations, in which anaphylaxis is discussed in its true perspective as part of the immunity response [9]. In some species the mast cells are caught up in the train of events that accompanies the union of antigen and antibody. It is equally clear that in other species they are not.

MAST CELLS AND THE CONNECTIVE TISSUES

The above work, relating the mast cells to the maintenance of the fluidity of the circulating blood and to the participation of histamine in allergy and anaphylaxis, tended to ignore the evidence of the first sixty years of research which appeared to relate the mast cell to the connective tissues. Neither heparin nor histamine now seems likely to play the role for which it was originally cast. 'The investigator experiences a sort of uneasiness which becomes more and more acute. Slowly but steadily he begins to feel that an essential element is lacking in an interpretation, and that the fundamental idea has been misunderstood, thus making impossible a true understanding of the facts' [10]. Perhaps, therefore, we should reexamine the original hypothesis of Ehrlich, that the mast cell is normally concerned with events in the connective tissues.

In 1921 M. Staemmler [11] stated his belief that 'the mast cell is a unicellular gland of the connective tissues which, through its activity, elaborates the mucinous intercellular cement'. Since then numerous investigators have adopted some modification of this general concept, relating the mast cell to the formation or storage of intercellular substance [12, 13].

The most recent hypothesis of a local 'mast cell cycle' in the connective tissues is that the cycle begins with the production of hyaluronic acid by the connective tissue cells themselves, and that, functionally, the hyaluronic acid is concerned in bringing about an orientation of protein collagen fibrils. As organization of the fibrils proceeds, the now unwanted mucopolysaccharide is removed enzymatically and is built up into a compact, sulphated form (heparin) in the granules of tissue mast cells [14]. Thus, the building blocks of a hydrophilic colloid, hyaluronic acid, are stored locally in dehydrated form as heparin. In this view, the sudden release of granule substance, still sulphated, into the blood stream of a dog is something of an accident. Normally, heparin is drained by the lymph channels. The main lymph channel in the dog is the thoracic duct which leads directly from the 'shock organ', the liver, to the blood stream. Looking back on events, we see how disproportionately this dramatic event in the dog has influenced all our thinking about the possible function of heparin in other species. The dog is the exception, not the rule, with respect to the function of its mast cells.

Faced with an alternative, Ehrlich seldom chose the wrong hypothesis. Time may yet prove that he was correct in his appraisal of the mast cell as a functioning component of the connective tissues.

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Historians and the scientific revolution

A. C. CROMBIE

In the nineteenth century, historians were greatly preoccupied with constitutional and political history and it is only comparatively recently that their attention has increasingly turned to considerations of social, economic, scientific, and technological factors. The growing tendency to regard the whole of civilization as the proper province of the historian is not, however, without precedent, for many eighteenth-century historians were inspired by the same idea. This article discusses how, and why, views about the significance of science and technology in historiography have changed from the Renaissance to modern times.

To a generation made more aware than any previous one of the division between science and the humanities, there is a particular interest in the treatment of the scientific revolution by the earliest modern historians to discuss the history of science. As observers living during or just after the event, writers of 'philosophical history' from Francis Bacon to Voltaire set out to give a systematic account, for an educated person, of the scientific movement as a revolution in ideas, methods, and attitudes: they tried to show how science had emerged in the history of civilization. In doing so, they gave analyses both of the nature of scientific thought itself, as they saw it, and also of the conditions that favoured or discouraged its progress; these analyses have left their mark on subsequent conceptions of the history of science down to the present day. The writer who most comprehensively summed up the whole of this early conception of the scientific revolution as an historical event was Voltaire [1]. A product of the age in which both modern science and modern historiography reached maturity, Voltaire was not only the first systematic historian of civilization and the first to make extensive use of the comparative method, but also the first historian to treat the history of science systematically as part of the history of civilization.

The view of the scientific movement that Voltaire incorporated into his systematic reconstruction of history came in the first place largely from the publicists of science, especially Francis Bacon and Fontenelle, and from the great scientists themselves. But he also used a view of history that had originated with the humanist historians of fifteenth-century Italy and had become modified by science at the end of the seventeenth century, in the controversy between Ancients and Moderns. Voltaire presents a picture of the historical consciousness of an age in which all educated people shared a common background in the humanities and in which science had recently become established as an essential part of general culture. He gave expression to what many thought, or were ready to think.

The view of history into which all the early modern historians fitted the origins of modern science was based on a specific conception of a great revival in European civilization between the fifteenth and the seventeenth centuries. By Voltaire's time the conception had gone through three main stages of development: humanistic, religious, and scientific.

The concept of a renaissance in the fifteenth century, after a thousand years of 'dark ages' following the fall of Rome, was developed during the Renaissance itself [2]. In the fourteenth century, Petrarch—inspired by a romantic admiration for pagan Latin literature, the city of ancient Rome, and the ideal of republican virtue—had divided history into 'ancient', before Constantine's adoption of Christianity, and 'modern', the long succeeding period of barbarism and darkness that had continued to his own time. From the end of the fourteenth century, humanist historians of art and of the Italian city states, especially of Florence, added to this division of history the notion of a recent revival, the beginning of which they often placed in the thirteenth century. During the same time, in Germany, Nicholas of Cusa introduced the term 'middle age' [3].

From the first, this conception of a period of antiquity, a middle period of barbarism, and a recent revival was far from merely descriptive; it was an historical judgment that influenced contemporary action. For example, the fifteenth-century Florentine historian Leonardo Bruni, who first explicitly used this division in political history, interpreted the recent political progress of his city as a revival of the model of republican Rome.

In 1483, Flavio Biondo, a papal secretary and student of the monuments of ancient Rome, defined the chronological boundaries of world history, with A.D. 410 to 1410 as a period distinct from those preceding and following it. Other Italian historians, especially Machiavelli, were even more precise in their use of history for contemporary political purposes. Historians of the arts, in presenting the contemporary development of painting, sculpture, and literature as a revival of classical models, wrote to encourage the new styles: they knew little, and cared less, about medieval Latin literature and the Gothic art beyond the Alps. Giovanni Villani, writing at the end of the fourteenth century, mentions no poets for nine centuries before Dante and no artists before Cimabue, who recalled art to nature, and Giotto, 'who surpassed the illustrious painters of antiquity in skill and genius'. Practising artists like Ghiberti and Alberti were content to accept this account of their relation to the past, and in the sixteenth century Vasari's term for the new style, *la rinascita*, became finally established.

The humanist historians made the conception of a revival, leading on to new conquests, an explicit part of their historical thinking, but half-consciously it had for long been an element in the restless mentality of the 'barbarians' who had entered into the lands and heritage of the western Roman Empire. It began to be expressed by writers in the twelfth and thirteenth centuries who could observe the effects on intellectual life of the translations then being made, from Greek and Arabic into Latin, of scientific and philosophical works, and who were witnessing also a modest technical revolution in the development of machinery for harnessing the power of wind, water, and draught animals, and in building, glass-making, metallurgy, surgery, navigation and other technical fields. In the twelfth century the French scholar Bernard of Chartres wrote: 'We are like dwarfs standing on the shoulders of giants, so that we can see more things than they, and can see further, not because our vision is sharper or our stature higher, but because we can raise ourselves up thanks to their giant stature' [4]. A century later, Roger Bacon could assert the progress of knowledge more confidently: 'We of later ages should supply what the ancients lacked, since we have entered into their labours, by which, unless we are asses, we can be aroused to better things, because it is most miserable always to use old discoveries and never to be on the track of new ones. Christians should . . . complete the paths of the unbelieving philosophers, not only because we are of a later age and should add to their works, but so that we may also bend their labours to our own ends' [5].

The activist attitude that is essential to the research mentality, prepared not simply to contemplate existing knowledge but to use it as a base for further advance, can be seen in formation in the writings of scholastic philosophers, mathematicians, and scientists like Robert Grosseteste, Roger Bacon, Albertus Magnus, and Thomas Bradwardine; it is the motive behind the numerous proposals for scientific method with which the thirteenth and fourteenth centuries abound. Moreover, Roger Bacon anticipated his later namesake in giving an analysis of the 'causes of error' and of the stagnation of science in contemporary Christendom, including among the most important the neglect of mathematics and experiment and the under-valuation of true learning. The low opinion of medieval culture held by the humanists was based on literature and art rather than on science and philosophy, in which they at first took little interest. But both the scholastic and the humanist reformers applied the same activist formula to history, taking an attitude to the past determined by the needs and aspirations of the present and providing a programme for future action. Such an attitude seems to be a deeply persistent element in modern European historical thinking.

To the humanist doctrines of the Renaissance, the religious controversies of the sixteenth century added a new interpretation that was to become a second important element in later accounts of the rise of modern science. To justify their own position, both humanist and Protestant writers agreed in seeing the immediate past as a revolting spectacle of ignorance, superstition, and corruption, polluting the pure stream of style and doctrine that had existed in an earlier ideal period.

The connection between humanism, Protestantism, and the rise of modern science became established in historical doctrine at the end of the seventeenth century, when each movement was seen as part of a common revolt against authority —the authority of scholastic education which still dominated the universities, the authority of the Church, the authority of Aristotle. The humanists turned from the 'dog' Latin and barbarous jargon of the scholastics to the pure style of classical literature, especially of Cicero. The Protestants turned from the institutionalized priestly guidance of the medieval Church to the plain text of Scripture and to private judgment of

its meaning, such as they held had existed in the primitive Church. The scientific reformers appealed first from medieval 'corruptions' to the pure Greek text of Aristotle, Galen, or Ptolemy, and later from these texts to direct observation of nature such as had been practised in Greek times. The complete doctrine was succinctly expressed by the American writer Cotton Mather in his 'American Tears upon the Ruines of Greek Churches', published in Boston in 1701: 'Incredible darkness was upon the Western parts of Europe two hundred years ago: learning was wholly swallowed up in barbarity. But when the Turks made their descent so far upon the Greek churches as to drive all before them, very many learned Greeks, with their manuscripts and monuments, fled into Italy and other parts of Europe. This occasioned the revival of letters there, which prepared the world for the Reformation of Religion too, and for the advances of the sciences ever since' [6]. Doctrine of the same form is found in Pierre Bayle's 'Dictionary', which was published in 1695 and was the source of many of Voltaire's historical opinions.

The need of the innovating parties in the literary and religious controversies to define their position in relation to the immediate past, affected the historiography of science rather by the general attitude taken by these scholars than by any special interest they had in science. Humanist editors of Archimedes or Aristotle were more interested in establishing a good Greek text or making a good Latin translation than in the mathematics or biology the texts contained.

Early in the seventeenth century a new group of scientific commentators upon history arose, with a completely different outlook upon the past and the future. These writers, Campanella, Francis Bacon, Descartes, and their followers, mark the third major stage in the conception of history that was to find full expression in Voltaire. They combined a full measure of contempt for the medieval past with an entirely new estimation of the importance of the scientific revival. Like their predecessors, they made their interpretation of history in the interests of a contemporary movement of which they were spokesmen. But they were in general unsympathetic towards the humanist and religious reformers, except in so far as these prepared the ground for science; their controversies they were inclined to find either uninteresting or unintelligible. They held that the new science was something essentially different from anything found in classical antiquity, let alone the barbarous middle ages; something which they themselves were adding to civilized life. Their attitude was similar to that taken by some sixteenth-century artists to the relation of their own work to classical models. Writing more and more in the vernacular, the new exponents of science stressed the material benefits brought by science and rational technology, 'the recent inventions of typography, cannon, and the mariner's compass' [7], the advances in industry, commerce, geographical discovery, and medicine. Knowledge, as Francis Bacon was most emphatic in pointing out, was the source of power over nature. The age began to bristle with works on scientific method, and with schemes for scientific utopias such as Campanella's 'City of the Sun' (1623) and Bacon's 'New Atlantis' (1627). Explanations of the past stagnation and current activity in science were used to devise formulae for future progress. Common to them all was the stress laid, in varying degrees, on experiment, mathematics, and the usefulness of science.

The most influential of these early seventeenth-century analyses of the history of science and of contemporary science were undoubtedly those by Francis Bacon and Descartes. Their accounts were complementary and comprehensive, and they became the starting points for disagreement as well as for development. Bacon stressed experiment and utility; Descartes stressed mathematics and utility. This combination provided the standard two-fold formula for future progress. Both writers used history, in Sir Walter Ralegh's phrase, 'to teach by examples of times past, such wisdom as may guide our desires and activities' [8]. In the case of both, the key to their conceptions of scientific method can be found in their view of the history of science. In his peremptory references to the history of philosophy, Descartes describes how he found that only in mathematics, pure and applied, had there been any grasp of truth [9]. His analysis of scientific method was aimed at realizing the ideal of a 'universal mathematics' embracing all the sciences. Bacon analysed the history of science much more thoroughly than Descartes and offered the first detailed modern sociological and historical analysis of the causes and conditions of scientific progress and decline.

In 'The Advancement of Learning' (1605) Bacon divided the study of human history into three kinds—civil, ecclesiastical, and literary—each with its own sources and problems. Of the third aspect of history he wrote: 'a just story of

learning, containing the antiquities and originals of knowledges, and their sects; their flourishings, their decays; with the causes and occasions of them throughout the ages of the world; I may truly affirm to be wanting. The use and end of which work I do not so much design for curiosity; but chiefly for a more serious and grave purpose, which is this, in few words, that it will make learned men wise in the use and administration of learning' [10].

Bacon complained in the preface to the never-completed 'Great Instauration' that in the intellectual sciences there was no search for new knowledge. The mechanical arts had shown some progress, because they were by their nature in close touch with experience and practice, but experiment, the essential method of discovery, had not been properly conceived. Philosophers had spun out general systems with too little reference to facts, and 'mechanics' were only interested in particular technical problems and did not search for causes: Bacon believed that they should combine their interests. Bacon's new experimental science was a method of acquiring knowledge that would provide both explanations of nature and a rational basis for technology.

Bacon's analysis, in the 'Advancement of Learning' and the *Novum Organum*, of why science had not progressed in the past provided later historians in the seventeenth and eighteenth centuries with their basic views on the subject. He said that the sciences had flourished during only three short periods of history: among the ancient Greeks, among the Romans, and, recently, among the nations of Western Europe. But even in those relatively favourable periods, scientific progress had not been as great as it should have been. Besides the lack of understanding of the experimental method and of an effective approach to the 'inquisition of nature', he emphasized the lack of opportunity for a proper scientific education, of a scientific profession commanding proper respect and position, and of government interest in science [11].

Bacon's attitude to the history of science, his claim that his analysis had not only exposed the mistakes of the past but also provided the means of avoiding them in the future, above all his emphasis on the past neglect of experiment and the dangers of philosophical systems and his optimism for the future of scientific discovery and its applications, all influenced the outlook of the founders of the Royal Society and contributed to the emotional energy behind their enterprise. They criticized Bacon for his neglect of mathematics, but they soon remedied that themselves. The same combination of beliefs and attitudes can be found in the *Académie des Sciences*. By the end of the seventeenth century, the Moderns were able to use the recent progress of science to convince the public of the superiority of modern over ancient achievements in the arts and sciences. The scientific revolution was seen as the most important part of the recent revival of the West. 'Is it not evident', John Dryden wrote in 1693, not in a scientific work but in his 'Essay of Dramatic Poesy', 'in the last hundred years (when the study of philosophy has been the business of all the Virtuosi of Christendom), that almost a new Nature has been revealed to us?—that more errors of the school have been detected, more useful experiments in philosophy have been made, more noble secrets in optics, medicine, anatomy, astronomy, discovered, than in all those credulous and doting ages from Aristotle to us?—so true is it, that nothing spreads more fast than science, when rightly and generously cultivated.'

During the second half of the seventeenth century and the first half of the eighteenth, the new science radically changed the type of culture of educated Europeans. Science began to develop as one of the learned professions, earning respect and sometimes reward, especially in France where the government gave direct support. Fontenelle popularized the scientific movement; books on botany were written for young ladies and on mathematics for the general public; Voltaire made important contributions to literature with his exposition of English empirical philosophy and science in his *Lettres philosophiques* or *Lettres sur les Anglais* (1734), and with his exposition of Newton's natural philosophy. Leading writers on many subjects—such as Locke, Hume, Montesquieu, Rousseau, Diderot, Condorcet—studied science seriously, and explored the possibility of extending its methods—now widely regarded as the only sources of certain knowledge—to all aspects of human life, behaviour, and history.

These interests and attitudes initiated the first detailed study of the history of science and of science as part of civilization. Leibniz, following Bacon, had proposed writing a history that would include science, literature, and religion as well as politics. In the preliminary discourse of the *Encyclopédie*, Diderot wrote in 1751 that the 'historical exposition of the order in which our sciences have followed one another will enlighten us and direct us how to transmit the principles of

these sciences to our readers'. The next year, 1752, saw the publication of Voltaire's *Siècle de Louis XIV*, followed in 1756 by his *Essai sur les mœurs et l'esprit des nations*, written to convince his friend Madame du Châtelet, the translator of Newton's *Principia* into French, that the study of history could be as interesting as that of mathematics and natural science, and could give rise to principles of equal importance [12]. In these works Voltaire set out to give an example of history written '*en philosophe*', to discover the causes of progress and decline, and to teach by the results. Science had provided him with a model of analytical and comparative methods of investigation; in return, he included in his comparative history of civilization a description of the history of science and technology.

Other historians in the second half of the eighteenth century, notably Hume, Robertson, Gibbon, and Condorcet, gave similar recognition, albeit sometimes perfunctory, to the influence of science and technology in history, and the same period saw the appearance of the first histories of particular sciences. A history of medicine by Daniel Le Clerc had been published in 1696; the publication of J. F. Montucla's great *Histoire des mathématiques*, in fact a history of the physical sciences, in 1758, was followed by that of other works of varying value. At the end of the century and in the early nineteenth century, the succession continued with the historical writings of Laplace, Cuvier, Thomas Young, Delambre and, later, of Guglielmo Libri and of William Whewell.

But by this time the general character of historiography had changed: it had become more accurate, but also more restricted. The eighteenth-century historians whose outlook had been formed by the intellectual revolution of early modern times may have seen history in the mirror of their own aspirations. They drew from the new science their model of rational investigation; in repaying their debt, by making the history of science and technology part of the history of civilization, they may have written polemically in order to extend the reign of 'reason' in their own day. The political and constitutional historians who dominated nineteenth-century historiography no longer felt that debt and they made history into the history of government. One reason for this may have been the influence of the classical seminar in German universities on the nineteenth-century conception of historical research. At the same time there was a hardening of the division in university education between science and the humanities. Classically trained historians excluded from their consideration all aspects of life not conventionally included among the humanities. Also, during this formative period of nineteenth-century historiography, the general upset in the structure and concepts of government following the revolutionary wars in Europe, and the business of acquiring and governing empires, gave constitutional and political history an immediately topical and practical interest.

Historiography must perhaps always reflect the problems of its own time. The character of life in our own day gives a new relevance to the eighteenth-century historians whose view included the whole of civilization. The present interest in social, intellectual, and scientific history and in the comparative method are in a sense a return to the ideas with which mature modern historiography began in the age of Voltaire. Once more, historians in their analyses of human behaviour and human society are seeking enlightenment from all aspects of civilized life. Historiography is again becoming the study of civilization as a whole, with the potentiality of providing a bridge, instead of reflecting a division, between the scientific and humanistic sides of our education.

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The zodiacal light and its interpretation

D. E. BLACKWELL

The zodiacal light, a cone of light extending along the zodiac, has been recorded since the seventeenth century, but has only recently been carefully investigated. The source of the light is still uncertain, but one interpretation has led to the hypothesis of an interplanetary gas. The author, who has just returned from the Andes, where the light may be much more conveniently observed than in Europe, describes in this article the light and the theories of its origin, and discusses the evidence concerning the existence of an interplanetary gas.

The zodiacal light, a permanent feature of the evening and morning sky, has been investigated on a few occasions during the last three centuries, but, except during the last decade, has never excited much interest among astronomers. It may be seen in the evening after the end of twilight, when the depression of the sun exceeds 18°, as a cone of light standing over the western horizon and extending along the zodiac. The cone is brightest near its base, where it is about 25° wide, and it gradually becomes fainter with increasing distance from the horizon; its brightness near the horizon approximates to that of the Milky Way, and in a very transparent sky it can be traced over a great circle of length 90°. As the earth rotates the cone remains fixed with respect to the Sun and is gradually carried beneath the horizon until only the faintest vestige remains a few hours after sunset. In the morning, the phenomena are repeated in the reverse order on the eastern horizon, the zodiacal light gradually becoming more prominent as the brighter parts appear above the horizon, until it is again most prominent when the Sun is 18° below the horizon. Thereafter, the dawn sky brightens and within a short time the zodiacal light can no longer be discerned. Its appearance soon after the end of twilight is shown in the photograph reproduced in figure 5; this was taken at a height of 17 100 ft by M. F. Ingham and the author during their recent expedition to the cosmic ray station of Chacaltaya in the Bolivian Andes.

There are occasional references to isolated observations in Europe and England during the seventeenth and eighteenth centuries. In March 1706, the Rev. W. Derham [1] wrote to the Royal Society from Upminster saying that he had 'spyed a very odd sort of Light in the Constellation of ♉ . . . I am sorry that the following Nights were cloudy; and although Easter-day Evening was fair, yet I forgot it unluckily then'. However, the first systematic study was undertaken by Cassini [2] at the Paris Observatory in 1683. The entry in his Journal for 10th June 1683 reads, '*Le Printemps de cette année* 1683, *a commencé par un spectacle des plus rares qu'on ait observé dans le Ciel*'. Cassini continued his observations until 1693. He realized that the zodiacal light maintains a constant orientation in space, but wrongly supposed that it is symmetrical about the plane of the solar equator. Its axis of symmetry is actually very close to the ecliptic—that is, the projection of the plane of the earth's orbit on to the sky—but as the angle between these two planes is never more than 7°, this mistake was easily made in these early observations.

The seasonal changes in the appearance of the zodiacal light in northern latitudes are shown in figure 1. The best view is evidently obtained when the ecliptic is standing most nearly vertical at the horizon, for then the brightest portions nearer the Sun may be seen; in northern latitudes this occurs in the evening during spring and in the morning during autumn. In southern latitudes it is seen best in the morning during spring and in the evening during autumn. The change of visibility with season was well understood by Cassini as his diagram, reproduced in figure 2, demonstrates. The Sun is shown depressed about 18° below the Paris horizon at the beginning of March, when it is south of the equator, and in June, when it is north of the equator. In June, when the zodiacal light is much less conspicuous, only those parts which are farther from the Sun, and therefore fainter, can be seen above the horizon and even these never rise far above the obscuring atmospheric layers near the horizon. However, Cassini was mistaken in drawing the zodiacal light during June narrower than in March.

Clearly, Northern Europe is not a suitable place for observation of the zodiacal light, because here the ecliptic is always far from the vertical. During

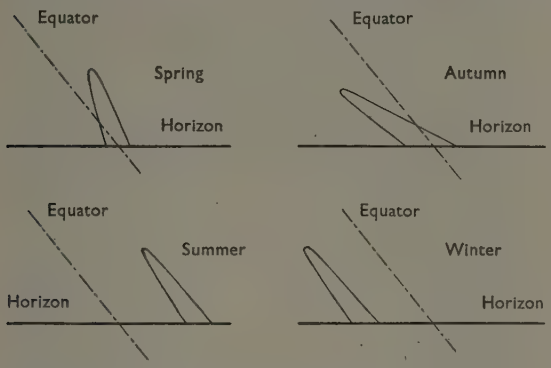

FIGURE 1 – *Seasonal changes in the appearance of the evening zodiacal light in northern latitudes.*

the most suitable season, and in good meteorological conditions, it can just be discerned in England, and even as far north as Scotland, but serious study requires an observing site in the Tropics where the ecliptic can stand vertical at the horizon. When such a site is also at a high altitude, say above 15 000 ft, where the atmosphere can be exceptionally clear, it appears astonishingly brilliant. Indeed, in the Andes it can be seen when the Sun is depressed only 12° below the horizon.

Cassini was convinced that the zodiacal light originates in interplanetary space and not in the outer parts of the terrestrial atmosphere, for he had satisfied himself that it shows no appreciable parallax. He suggested that it has its origin in a nebula surrounding the Sun which is physically related to the Sun and rotates with it. Part of this theory was based on his mistaken belief that the plane of symmetry of the zodiacal light coincides with the plane of the solar equator, but Laplace argued against it on the grounds that if this supposed cloud rotated with the Sun, centrifugal force would disrupt those parts of it beyond the orbit of the planet Mercury. However, other observers have been equally convinced of a terrestrial origin, and it is a remarkable fact that after three centuries there is still a dichotomy of opinion. In recent times the advocates of an interplanetary origin are H. Siedentopf [3], H. C. van de Hulst [4], and C. W. Allen [5]; those of a terrestrial origin are E. O. Hulburt [6], L. Vegard [7] and F. Schmid [8].

One argument for an interplanetary origin is that the zodiacal light appears to be simply an outer extension of the solar corona. This is suggested by figure 3, in which the brightness of both the corona and the zodiacal light are plotted on the same diagram as a function of angular distance from the Sun. The measurements on the corona are those of the author [9], made from an open aircraft flying at 30 000 ft during the eclipse of 30th June 1954. Those on the zodiacal light are taken from the work of F. E. Roach [10]. The more recent observations in the Andes will practically close the gap between the corona and zodiacal light data, but already it is clear that the two curves join naturally without any discontinuity.

Ten years ago, Allen and van de Hulst simultaneously and independently gave a more sophisticated argument for linking the solar corona and zodiacal light. It is now believed that most of the light of the corona has its origin in two mechanisms; within a $\frac{1}{4}°$ of the Sun's limb it is chiefly due to Thomson scattering of sunlight by free electrons, while scattering by interplanetary dust particles predominates farther out. This division of the total light into two parts was first made by W. Grotrian in 1934, when he called them the K- and F-components respectively. The dust responsible for the F-component cannot exist close to the Sun because there it would be evaporated by solar radiation. It follows that this component of the solar corona must be due to small-angle scattering by dust far from the Sun and relatively close to the observer, although still in interplanetary space, rather than to large-angle scattering, which is responsible for the zodiacal light (see figure 4). Allen and van de Hulst suggested that the scattering mechanism is none other than

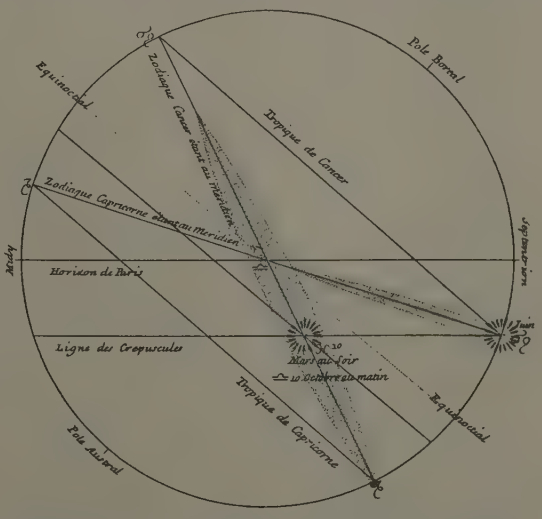

FIGURE 2 – *The zodiacal light according to Cassini (from* [2]).

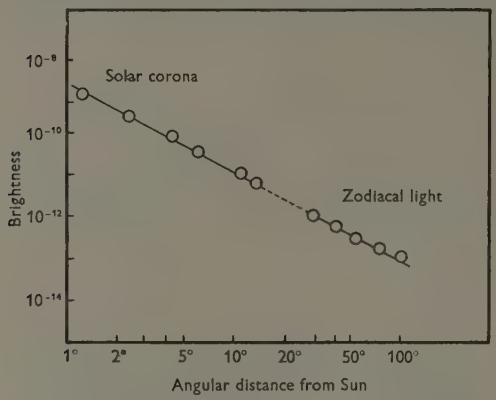

FIGURE 3 – *Brightness (measured in terms of the mean brightness of the solar disk) of solar corona and zodiacal light showing the relation between the two phenomena.*

diffraction by the smaller dust particles, so that the F-corona is analogous to the coronae which sometimes appear to surround the Sun and Moon when they are seen through thin cloud. From the absolute brightness of the F-component, and its variation with angular distance from the Sun, it is possible to calculate the concentration of all interplanetary dust particles between specified limits of size. It is usual to assume a size distribution of the form

$$N(a)\ da = Ca^{-n}\ da$$

where $N(a)\ da$ is the number of particles having radii between the limits a to $a+da$, and n and C are constants, and to suppose that this relation is valid between a lower limit of about 1 μ (all smaller particles are swept from the solar system by the pressure of solar radiation) and an upper limit which is in the neighbourhood of 300 μ. This theory gives the total number of particles with radii between these limits as about $2 \times 10^{-15}\text{cm}^{-3}$ or about 8 particles per cubic mile.

The zodiacal light is formed chiefly by reflection of sunlight from the interplanetary dust, rather than by diffraction, because it is at a greater angular distance from the Sun. Using the model for the dust cloud that has been derived from observation of the F-corona, it is possible to account for the brightness of the zodiacal light by assuming an albedo, or total reflectivity, for the dust particles of about 3 per cent. There is no evidence at all which can lead to an independent estimate of the albedo, but this derived value is a reasonable one. This conclusion, that it is possible to account for the properties of the F-corona and the zodiacal light over a wide range of distance from the Sun using one simple model for the interplanetary dust cloud, further supports the contention that the zodiacal light is formed in interplanetary space.

Careful observations of the zodiacal light when it is not too much inclined to the vertical show that its symmetry axis is slightly tilted with respect to the ecliptic. The star chart of figure 6 has been made from one of the photographs taken on the Andes expedition, and it shows that on this occasion the symmetry axis was displaced from the ecliptic by about one degree. Continuous observation throughout a year shows that the plane of the zodiacal light is closer to the average plane of the planetary orbits, which is inclined to the ecliptic at an angle of 1° 6′. This is a subtlety which cannot easily be explained by a geocentric theory, and for the remainder of this account we shall assume the more generally accepted and more reasonable interplanetary theory.

This was the situation in 1953 when Siedentopf started his investigation. He observed the zodiacal light from the Jungfraujoch, at a height of 11 000 ft, at latitude 46° N., and obtained the first reliable measurements of its degree of polarization for those parts more than 35° from the Sun [3]. The degree of polarization, p, is here defined as

$$p = (I_t - I_r)/(I_t + I_r)$$

where I_t and I_r are the intensities of the components of the light which have their electric vectors transverse and radial to the radius vector to the Sun. Figure 7 shows Siedentopf's measurements plotted as a function of distance from the Sun; in this diagram the points closer to the Sun than 35° represent observations made by the author from a flying boat in the Pacific area during 1955 [11].

The curve of figure 7 is the starting point of the modern hypothesis of an interplanetary gas, which

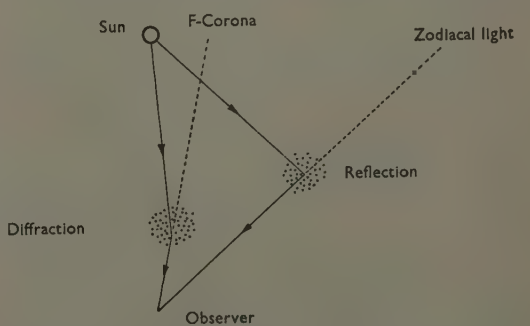

FIGURE 4 – *Origin of the F-component of the solar corona (diffraction scattering) and the zodiacal light (reflection).*

FIGURE 5 – *A photograph of the zodiacal light taken from the cosmic ray station of Chacaltaya in the Bolivian Andes at a height of 17 100 ft. A simple lens of relative aperture f/1·8 and focal length 5 in. was used. The exposure time was ten minutes.*

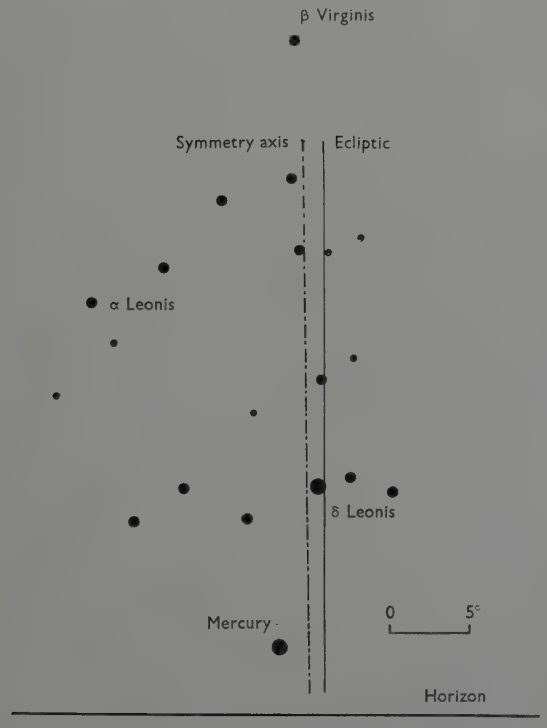

FIGURE 6 – *Position of the symmetry axis of the zodiacal light in relation to the ecliptic.*

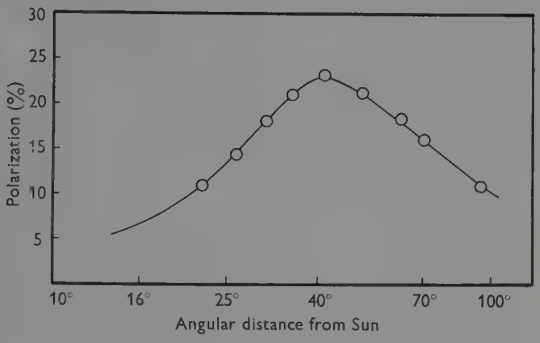

FIGURE 7 – *Degree of polarization of the zodiacal light as a function of angular distance from the Sun.*

is still less than a decade old. We shall now describe the apparently good evidence for the existence of this gas, but we must give a warning at this stage that more powerful arguments against its existence will be suggested later in this article. Siedentopf suggested that the maximum polarization of 23 per cent observed at a distance of 35° from the Sun is too great to be explained by dust scattering alone. It is very difficult to predict the degree of polarization of light scattered by the interplanetary dust because it depends upon such properties of the dust particles as their material, shape, and surface texture, all of which are quite unknown; but Siedentopf considered that the polarization is likely to be close to zero. If this is correct there must be gaseous material in interplanetary space which is scattering highly polarized light. Further, the scattering cannot be by neutral atoms, for these would scatter according to Rayleigh's λ^{-4} law and give a 'blue zodiacal light', whereas it is known that the energy distribution in the zodiacal light spectrum is practically the same as that in the solar spectrum. A remaining possibility is scattering by a cloud of free electrons. Such a cloud will scatter highly polarized light; the actual degree of polarization can be calculated once the electron distribution is known, but as a rough estimate it may be taken as 50 per cent. Assuming that the polarization of the dust component is zero, and knowing that the total observed polarization is about 23 per cent, it is now possible to calculate the relative contributions of dust- and electron-scattered components in the zodiacal light; the result is that the two contributions are approximately equal. The next step is to calculate the number of electrons per cm^3 in interplanetary space, using the Thomson theory of electron scattering. The result of this calculation is that at 1 A.U. from the Sun (equal

to the distance of the Earth from the Sun) there are about 10^3 free electrons per cm^3.

If this gas really exists, it is detectable in these regions only because it is highly ionized and the resulting free electrons are scattering a feeble proportion of sunlight to the observer. However, the foregoing argument is not convincing by itself, for it rests upon the very doubtful assumption that the light scattered by the interplanetary dust is not polarized, and were it not for the existence of several other lines of evidence, all leading to the same conclusion, it would have been dismissed as unprofitable. That the existence of such an interplanetary gas is not unreasonable is shown by the graph of figure 8, which shows the variation of electron density in the solar corona with distance from the Sun. The data for this diagram have been deduced from measurements made during total solar eclipses, those in the range from 8 to 20 solar radii (0·036 to 0·10 A.U.) are results from the high-altitude eclipse observations already mentioned. An electron density of $10^3\ cm^{-3}$ at 1 A.U. is evidently a not unreasonable extrapolation of the eclipse curve.

The first suggestion that the electron density in this region might be high came from the solar accretion theory of Hoyle, Lyttleton, and Bondi [12] in 1946, six years before the work of Siedentopf. These authors attempted to explain the existence of the solar corona by supposing that interstellar gas is being drawn into the Sun by gravitational attraction. This gas gradually increases in density as it approaches the Sun, because it becomes more confined, until at 1 A.U. the density may be expected to be about 10^3 atoms per cm^3. As the interstellar gas is probably composed chiefly of hydrogen, which will be almost completely ionized in this region, this value implies an electron density of 10^3 electrons per cm^3. Thus, the prediction of the accretion theory was apparently verified six years later by Siedentopf's zodiacal light investigation.

More support for the hypothesis of an interplanetary gas came from an unexpected source. It was shown by Storey, who was then working in the Cavendish Laboratory Radio Group at Cambridge, that radio measurements could give the electron density in the Earth's ionosphere at heights of up to several earth radii. Storey was investigating the problem of 'whistling' atmospherics—those atmospherics which are detected by a radio receiver as a whistle instead of a crackle. Such atmospherics are propagated towards the observer along a path which lies chiefly

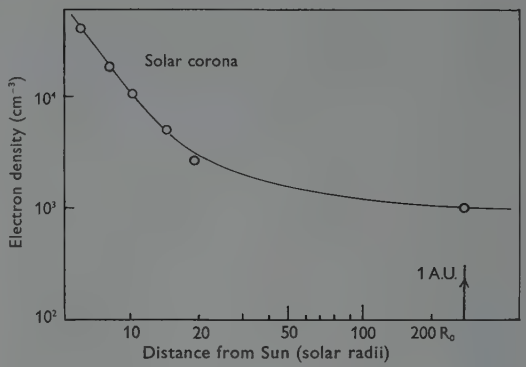

FIGURE 8 – *Variation with distance from the Sun of electron density in the solar corona.*

in the ionosphere, with a speed that depends upon the frequency; hence the different frequencies contained in the burst of radiation arrive at the receiver at different times, producing a whistle. The effect depends upon the electron density and geomagnetic field along the path and can be used to measure ionospheric electron densities. By 1954 density determinations had been made by this method to a distance of about 1·7 earth radii from the Earth's surface, giving the value of about 10^3 at this extreme distance. This position in space was so far from the Earth that the value for the density was assumed representative of interplanetary space and therefore further supported the Siedentopf value.

By 1956 there was almost universal belief in the existence of the interplanetary gas and there was a growing body of theoretical work on its expected properties. The theory of Chapman is important here; it begins by calculating the thermal conductivity at each place, from kinetic theory considerations, and hence the temperature distribution. The theory then assumes that the gas is in gravitational equilibrium, so that the temperature distribution leads directly to the density distribution. The calculated density at the distance of 1 A.U. from the Sun is about 10^3 electrons cm^{-3}.

We have now seen that there are four completely independent lines of evidence for the supposition that the electron density at 1 A.U. is about $10^3\ cm^{-3}$. Each piece of evidence is, by itself, rather weak, but when all are considered together they form a fairly convincing picture, especially as the supposed electron density is a reasonable extrapolation from the densities in the solar corona. However, there are equally convincing arguments against the existence of a gas of this order of density; only two will be mentioned here.

The first argument concerns the polarization of the dust component of the zodiacal light at angular distances from the Sun greater than 30°, which correspond to linear distances of greater than 0·5 A.U. or 108 solar radii. If it is assumed that the electron density curve is known as far as 2 A.U. from the Sun, then the observations of total polarization of the zodiacal light can be used to calculate the polarization of the dust component only, as a function of angular distance from the Sun. Alternatively, if this polarization curve for the dust component is assumed, then the variation of electron density with linear distance from the Sun in this region can be computed. The results of these calculations may be described very briefly. They are, first, that if an electron density distribution of the form shown in figure 8 is assumed, then the polarization of the dust component of the zodiacal light must be negative at large elongations; this is not physically impossible, but very unlikely. Second, if a reasonable polarization curve for the dust component is assumed—that is, one which is greater than zero at all elongations—then the electron density curve shows an abrupt cut-off at about 1·2 A.U. Again, this is not impossible, but rather unlikely. The easiest way out of the difficulty is to suppose that the electron component does not exist and that the observed polarization is virtually that of the dust component alone.

The second argument concerns the plane of symmetry of the zodiacal light. It has already been remarked that this is very close to the plane of the ecliptic. If it is supposed that the plane of symmetry of the dust component alone is very close to the ecliptic, then it follows that the plane of symmetry of the electron component is also close to the ecliptic. But, electromagnetic forces, even of minute interplanetary magnetic fields, acting on a free electron cloud completely dominate the weak gravitational forces which would otherwise cause it to become nearly symmetrical about the ecliptic. Again, the only way out of this difficulty is to suppose that the electron component is of negligible intensity.

An attempt was made recently by M. F. Ingham and the author, during their expedition to the Andes, to detect the supposed interplanetary electrons by an independent method. Basically, the method uses a spectrum of the zodiacal light. If the zodiacal light is caused by dust scattering alone, it may be expected to have a spectrum identical with that of the Sun. On the other hand, if the interplanetary electrons really exist they probably have a high kinetic temperature, as was first shown by Chapman, and the sunlight scattered from them should show a continuous spectrum. Hence the two possible components may be separated by comparing the zodiacal light spectrum with the solar spectrum. These two spectra were obtained at Chacaltaya, but only a preliminary comparison has been made so far; the tentative conclusion is that the electron density at 1 A.U. from the Sun is much lower than the value of 10^3 cm^{-3} previously supposed, and that the zodiacal light is due largely to dust scattering. This implies that the four arguments previously given to demonstrate the existence of interplanetary electrons are faulty; indeed, recent radio measurements have shown that the electron density at five earth-radii from the Earth is about 250 cm^{-3} only.

This result has been largely confirmed by the recent observations made by Soviet scientists using the first space rocket, launched on 2nd January 1959. This rocket, which went into orbit around the Sun, was equipped with apparatus for direct measurement of interplanetary gas density. Measurements made at distances of 150 000 km, showed a concentration of interplanetary particles in the region of 300–400 positive particles cm^{-3}.

It should not be supposed, however, that the subject of the zodiacal light is now closed; we have described here only one of its aspects, and there is much still that is not understood.

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Schizophrenia and the psychotomimetic drugs

J. P. DEWSBERY

Schizophrenia is a mental disease that is extremely resistant to treatment, and it is one that affects almost one per cent of the population. Recent studies of drugs that produce symptoms closely similar to those of schizophrenia have suggested a number of theories concerning the origin of the disease. The research, and the new theories, are discussed in this article.

Increases in therapeutic effectiveness that have been introduced in the last two decades, especially in the treatment of infective disorders, have thrown into sharper relief the failure of medical research to solve the problems of insanity. It is only in recent years that the public and Parliament have seemed to realize the burden of mental illness carried by our society. The mental hospitals of Great Britain have a standing population of 150 000 and, since 45–50 per cent of this represents chronic mental illness, it does in fact involve, in the product of numbers of patients and years spent in hospital, a terrible total of incapacity and suffering. Though the various forms of depression can now be more effectively treated than they were, the condition schizophrenia remains as the principal cause of chronic mental illness, and this is relevant to our topic in that schizophrenia is the condition most nearly simulated by the states of intoxication produced by hallucinogenic drugs. It is a condition which, as implied by its older name, dementia praecox, tends to come on early in life, well over 50 per cent of the cases manifesting themselves for the first time between the ages of 15 and 25. The onset of the condition is gradual and imperceptible, in the sense that the early symptoms of social withdrawal and a lessening of activities involving the outside world are not, especially in the minds of lay people, associated with the idea of insanity. It is only when gross disorders such as delusions and hallucinations make their appearance that a certain diagnosis can be made, and it is these symptoms, particularly the hallucinations, that are simulated by the mental states artificially produced by hallucinogenic drugs.

Speculation on the cause of schizophrenia leads to three alternative postulates:

1. It is the result, as some forms of psychoneuroses are believed to be, mainly of environmental conditions to which the patient had become subjected in the earlier and formative years of life, that is, it is psychogenic.
2. It is due to some structural abnormality of the brain.
3. It is due to some chemical abnormality in a brain that is itself structurally normal.

There is little evidence in favour of the first view. A great deal of very careful work has been done in search of support for the second view with results that are so far inconclusive [1]. The purpose of this article, however, is to review the third of these possibilities, especially in the light of work done with the hallucinogens.

Historically, it has for long been held that in schizophrenia the causative factor is an unknown toxic substance. This was the view of the classic writers of continental psychiatry, such as Kraepelin and Bleuler. Despite this, a century of biochemical research has failed to implicate any particular substance or even, until quite recently, to demonstrate any particular metabolic anomaly in schizophrenia.

However, knowledge of substances that produce in normal people mental states that closely resemble the disorder has kept alive a hypothesis that might otherwise have been abandoned for lack of evidence. These substances, also known as schizogens, or more precisely, psychotomimetic agents, are being increasingly used in the production of what have aptly been called 'model psychoses'. These states are of value, firstly, because they give the student himself an approximate subjective experience of what mental disorder is like; secondly, because they can be studied in the same way as true mental disorders; and thirdly, because a study of the chemical nature of the hallucinogens can be expected to throw some light on the nature of the hypothetical substances believed to cause mental disorder.

The sort of symptoms experienced in the model psychoses produced by these drugs are distortions of reality, of either a simple or complex order. Thus in the early stages of the intoxication there may be a feeling of bodily lightness that later develops into gross disturbance of the perception of the bodily self, in which the limbs or the whole body may feel huge or minute, or in which the self seems to be dissociated from the body and to watch it from some point external to it. Likewise there may be simple or complex distortions of external reality. These may take the form of visions of geometrical patterns in shifting forms, perhaps stimulated by real visual or auditory experiences, and may later be replaced by more complex disturbances in the form of distortions of faces or things, or hallucinations of highly coloured landscapes rapidly forming and dissolving. Over the entire psychotic experience may preside distortions of the time sense, so that centuries may seem to have passed in what was only an hour, or there is a sense of immense antiquity, as if one were in contact with some very much earlier era of civilization. Nevertheless, the subjects of these experiments hardly ever seem entirely to lose the sense of their own individuality, so that they are always able to see themselves from a small corner of the mind as undergoing an abnormal and artificially produced experience. When the sense of personal identity is lost, as it has been in some experiments [2], the experience is said to be a terrifying one.

An important feature of these experiments is that the experience differs in content from one individual to another. This is an important point, since one of the objections to the theory that schizophrenia may have a physical cause is that it is impossible to conceive of such a complex clinical picture being produced by simple physical means. Another view widely held is that schizophrenia is not really a unitary disease-concept in the way that, say, pulmonary tuberculosis is, but that it is really a group of disorders in which the resemblance is purely that of symptoms. Thus it is held that the grouping is based on superficial resemblances and that no such grouping would be justified if it were based, as the classification of all organic disorders is, on cause. However, the study of the model psychoses suggests that a closely related group of compounds, or even possibly a single compound, can produce the symptoms of the various types of schizophrenia. In other words, the individual differences in schizophrenic symptoms could be due to genetically determined differences between one nervous system and another, and to the differing life histories of the individuals up to the time of onset of the disease.

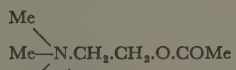
MODE OF ACTION OF THE HALLUCINOGENS

If these substances are to give a clue to the unknown toxic agent in schizophrenia, one would first look for some similarity between their chemical structure and that of any substances occurring in normal body metabolism. A special reason for this is the recognition, particularly during the last two decades, of the importance in biochemistry of antimetabolites. These are chemical substances which closely resemble in structure a normal chemical substrate to a particular reaction, involving, for example, an enzyme. By their similarity they get taken up by the enzyme, but are after that unable to perform, or only partially able to perform, the biological purpose of the substance they have displaced. In this way they 'block' the reaction and, if it is part of an anabolic or catabolic chain of reactions that is necessary for nerve-cell activity, interfere with the efficiency of the chemical process. Thus antimetabolites may interfere by blocking one of the nutrient reactions necessary to the maintenance of nerve-cell activity.

Yet another suggestion relates to the site of the action of antimetabolites. These substances prevent a particular biochemical reaction from occurring, and this would presumably be the point of action of the hypothetical toxic substance. The results could equally well be explained, however, by the simpler postulate that one of the normal constituents of the reaction, such as an enzyme, is absent, so that the anomaly is not the presence of a substance that should not be there, but the absence of one that should. This would put the disease on the same footing as a condition such as diabetes mellitus or one of the vitamin deficiency diseases (which in the case of B deficiency, incidentally, are accompanied by mental symptoms).

There is, however, still another hypothesis, that is in no way concerned with the nutrient activities of nerve tissue. The passage of an impulse along a nerve fibre is an electrical phenomenon and it had until recently been assumed that the passage of this impulse from the termination of the nerve fibres of one cell across the gap, the synapse, to the next nerve cell in the chain of conduction was also an electrical process. There is now considerable doubt about this [3] and an increasing body of evidence favours the view not only that it is a

chemical process by which a nerve impulse is conducted across the synapse, but that there are several different chemicals, each playing its own part in different types of synaptic conduction. It is certain that the transfer of a nervous impulse from the ending of a motor nerve across to the muscle takes place by means of a chemical transmitter, acetylcholine.



Acetylcholine

In order that the resultant muscular contraction should not outlive its period of requirement, an enzyme, cholinesterase, exists to destroy the acetylcholine. The disease myasthenia gravis, which is characterized by a paralysis of the muscles on exertion so that muscular contraction weakens with the repeated use of a particular muscle group, can be treated by the administration of a substance that partly blocks the destructive effect of cholinesterase. This process, though not directly relevant to mental illness is thought to be a working model of synaptic transmission. There is, in other words, increasing evidence that acetylcholine and other substances are responsible at higher nervous levels for the trans-synaptic conduction of nervous impulses. This has led to the postulation of different types of nerve endings according to the different substances supposed to play a part in their mechanisms.

Currently three substances are under scrutiny:

1. Acetylcholine.
2. Adrenaline and its near relative noradrenaline (epinephrine or norepinephrine).
3. Serotonin (also known as enteramine, 5-hydroxytryptamine, or 5-HT).

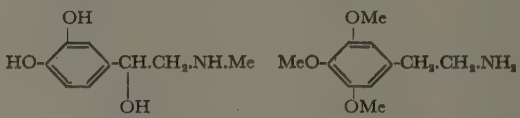
1. ACETYLCHOLINE

The mode of action of this substance has already been briefly described. The nerve endings at which it plays a part are called 'cholinergic'. Any substance which interferes in the reaction between it and cholinesterase will interfere with synaptic transmission.

Curiously enough, although this was the substance first proved to be a synaptic transmitter, most of the recent work has been not with acetylcholine, but with the two other substances, particularly serotonin. Di-isopropyl phosphorofluoridate (DFP), a blocking agent of cholinesterase, was the subject of some work in 1953 [4] but it is only recently that research has turned again to the antagonists of acetylcholine [5]. It seems likely that this will shortly become a growing-point once again in research into the hallucinogens.

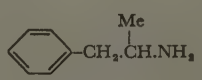
2. ADRENALINE

In 1952, H. Osmond and J. R. Smythies [2] drew attention to the possible significance of the well known resemblance between the structural formulae of adrenaline and mescaline.



Adrenaline Mescaline

Their postulate was that in schizophrenia some abnormal metabolite, possibly intermediate in structure between these two substances, might be produced in the body and so act as a toxic substance, or, as we would now say, act as an antimetabolite at adrenergic nerve endings. In their paper they referred to adrenochrome, a degradation product of adrenaline, and described some of the psychotomimetic effects of its administration. However, the follow-up of their hypothesis has so far not led to any conclusive results. This has not so much led to its abandonment as to its incorporation in larger and more complex hypotheses. Confirmation of the importance of the psychotomimetic role of adrenaline-like substances (sometimes referred to as sympathomimetic amines) has, strangely enough, come from another direction, namely from the discovery of a new form of drug addiction. D. Young and W. B. Scoville in 1938 [6] were the first to draw attention to the possible psychotomimetic effects of amphetamine, normally used for the treatment of, amongst other diseases, narcolepsy, a disease characterized by attacks of an irresistible urge to fall asleep. P. H. Connell [7] in a monograph on the subject reviews the literature and details the results of forty-two cases of psychosis that he himself had come across in his work. The relevance for this article was the very strong resemblance between the symptoms of amphetamine intoxication and schizophrenia.



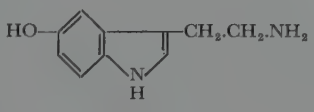
Amphetamine

So much for the evidence in favour of the psychotogenic effects of the sympathomimetic amines.

Pharmacologically, they appear to act as synaptic-blocking agents. A. S. Marrazzi [8] showed that if a particular point in one cerebral hemisphere were stimulated an electrical potential could be picked up at the corresponding point on the contralateral hemisphere. There is reason to believe that this involves a 2-neurone transmission process across the corpus callosum, the band of nerve tissue which anatomically and functionally unites the two hemispheres. Injection of either adrenaline or noradrenaline into the circulation just before stimulation was followed by a diminished response in the opposite hemisphere. Marrazzi's view is that adrenaline and acetylcholine have a reciprocal relationship in their effects on synaptic conduction, the one inhibiting, the other facilitating it.

3. SEROTONIN

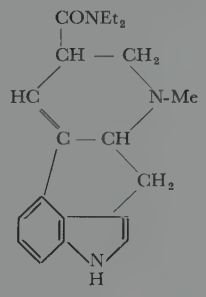
This substance was isolated by M. M. Rapport, A. A. Green, and I. H. Page in 1947 [9], in a search for substances in blood serum that exert a constrictor effect on the blood vessels. Page himself reviews its neurophysiology in a later article [10].



Serotonin

In addition to its vaso-constrictor properties, it was also found to have a constrictor effect on smooth muscle generally. A survey of its distribution in the mammalian body was carried out, one result of which was the discovery that it was present in considerable quantities in the brain, a discovery, incidentally, made at the same time and independently by A. H. Amin, T. B. B. Crawford, and J. H. Gaddum [11]. The latter showed that it was distributed in different parts of the brain in widely differing concentrations. The concentration was low in the cerebral cortex, and highest in the basal ganglia. These are groups of nerve-cells at the base and, from an evolutionary point of view, in the older parts of the brain and they are thought to regulate both visceral function and the emotions. By contrast, the cerebral cortex is concerned with the integration and interpretation of incoming sensory information, and with the initiation, either at once or after an appropriate delay, of the action necessary to meet it. Furthermore, the cerebral cortex is a part of the brain especially well developed in higher mammals. To complete the picture it should be added that the same differential distribution had also been shown for acetylcholine.

One of the most potent hallucinogens so far discovered is D-lysergic acid diethylamide (LSD-25).



Its discovery as a psychotomimetic agent was accidental, and occurred in 1943 when Hofmann, investigating ergot derivatives in the Sandoz laboratories at Basle, accidentally inhaled a small quantity of it. He was overtaken by a peculiar sensation of dizziness and listlessness and left for home in a dream-like state. 'With my eyes closed fantastic pictures of extraordinary plasticity and intensive colouring seemed to surge towards me'. As with the other substances, its psychotomimetic effects were discovered before its pharmacological ones. One of its most striking features is the minute concentrations in which it is effective as a psychotomimetic: as little as 0·5–1·0 micrograms can produce psychic effects in the human. It is thus some 5000 times more potent than mescaline.

It was Gaddum, however, who first investigated its pharmacology, and here too its potency was shown to be equally high. Serotonin causes contraction of smooth muscle preparations *in vitro* [12]. Gaddum demonstrated [13] that as low a concentration as 10^{-9} g/litre of LSD would antagonize this effect. The implications seemed obvious: the lysergic acid was acting as a blocking agent at a serotonin-activated synapse. This, however, is not the end of the story, since A. Cerletti and E. Rothlin showed in 1955 [14] that brom-LSD, in which a bromine atom replaces the hydrogen in the (2) position, while being even more potent in its blocking action than serotonin on smooth muscle preparations *in vitro*, has no psychic effects whatever. This apparent contradiction illustrates one of the difficulties now being tackled by workers in this field, namely a partial lack of correspondence between physiological effects, either *in vitro* or *in vivo*, on the one hand and psychic effects on the other, and nothing conclusive has yet been found.

CONCLUSION

The main purpose of this brief survey of work done for the most part in the last ten years, is to show the way in which certain substances, some natural, some synthetic, have been used to investigate the cause of schizophrenia. The underlying assumption is that the primary cause of the condition—or, as some would have it, the group of conditions—is a disorder of body chemistry, either inside or outside the nervous system.

If the disorder is in the nervous system, it may be a defect in one of the inter-related enzyme-systems which, concerned with the catabolism of glucose, provide the nutrient support to nervous activity in general. However, work with psychotomimetic drugs has tended to direct more attention to the biochemistry of the synapse, and, since this involves substances which can be produced outside the nervous system, such as in the adrenal glands or in the intestine, it cannot be said for certain where the site of the 'biochemical lesion' is. Indeed, it might be better to think of this anomaly as located not in any bodily organ so much as in a certain chemical process going on in the body as a whole. This leads to an aspect of research which barely comes within the scope of this article, and that is the study of body-fluids in schizophrenia. Since 1955 it has been known that ceruloplasmin, a copper-containing enzyme, shows fluctuations in blood level corresponding with changes in the degree of mental disturbance in schizophrenic patients. It can even be shown to vary in normal people undergoing schizophrenic-like states artificially produced by the psychotomimetic drugs. However, these variations are not peculiar to schizophrenia, and occur in quite a number of other conditions in which there are no mental symptoms. Arising out of this work is research into 'taraxein' [15], a substance present in the serum of schizophrenics which, injected into normal people, will produce transient schizophrenic-like symptoms. The mode of action of this substance is at present under investigation.

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The British Association for the Advancement of Science

Last September the British Association for the Advancement of Science returned for its annual meeting to York, where the inaugural meeting was held in 1831. The nature of the scientific world has changed enormously since then, and the task of the Association has changed correspondingly. To meet these changes the Association has had to set about helping the advance of science in new ways. Originally, it saw its aims in terms of making the latest scientific discoveries known to an audience composed largely of scientists, and of convincing the government of the importance of science to the community. It was at these annual meetings, then by far the major activity of the Association, that the world first heard about, for example, Crookes's researches that led to the modern cathode-ray tube and Sir William Ramsay's discovery of argon. The pace of science is now too rapid for scientists to wait upon an annual meeting to announce their progress, and journals, vastly more numerous than in 1831, exist for this purpose. Although they need guidance on policy, governments no longer need to be persuaded of the fundamental importance of science. Again, the British Association came into existence to make the 'cultivators of science acquainted with one another.' The effect of the departmentalization of science has been to emphasize the importance of international conferences of those working in specialized fields of science, and it has become increasingly difficult—desirable though it is—to assemble large meetings of scientists of different disciplines.

The progress of science, and of its utilization, depends upon having the support of a public that appreciates its results, and upon having a steady stream of new scientists, and it is to the task of ensuring the existence of these that the Association is now particularly turning its efforts; this has always been part of its function, but its relative importance has enormously increased. In 1831, long before the introduction of compulsory education in Britain, the educated public was a small minority of the population, and its circumstances were such that it was feasible to arrange large conferences to tell people of the progress of a science that was sufficiently unspecialized for them easily to comprehend its significance. The public that one wants to appreciate science has now become the whole nation; the science they are to appreciate is now so complex as to need for its clear exposition scientists with special gifts. The British Association has evolved, especially in the last few years, so as to be of value in this new climate.

One notable change concerns the annual meeting. A nineteenth-century newspaper, reflecting the general antipathy to science, unkindly suggested that having the annual meeting at a different place each year would enable it to take place somewhere where 'the scandal of former fooleries may not have reached.' The actual purpose, and effect, of having a different meeting place each year was to bring the Association into close contact with new groups of people: inevitably, though, any particular centre would be visited only once in every thirty years or so, which is today far too infrequently.

To overcome this difficulty, a number of local Area Committees have been formed throughout Britain, usually in association with the existing organizations for adult education or with other local groups. Lectures by visiting scientists have been so well received that the scheme is being extended. For parts of the country where it has not yet been possible to set up Area Committees, a central lecture service has been set up, aimed at supplying a lecturer on any scientific subject at any time to groups anywhere in Britain.

The lecture system has been an outstanding success, in the sense that a large number of lectures have been given to widely varied audiences, incidentally at very low cost. It has meant that the public has been able to hear authoritative statements on subjects on which it feels a need to be informed. The subjects chosen—nearly half the lectures were on atomic energy, nuclear physics, and radiation hazards, biological subjects being the next largest group—show that a substantial section of the British public is anxious to learn about matters of national importance that have a scientific background. By its nature, an annual meeting lasting a week is likely to attract largely an audience whose leisure is either dedicated to science or is not severely limited: in fact, the Association found, from a questionnaire completed by those attending a recent annual meeting, that a very high proportion of members worked at

either universities or schools. By contrast, the audience at local lectures represents a very much broader section of the population, and the number of people reached is very large.

The Association has broadened its activities not only horizontally but vertically. The future of science, and of the nation, depends upon a sufficient supply of young people interested in science, as its future scientists, and aware of the value of science, as its administrators and citizens. The past year has seen the start of a more lively programme for young people, which included a Junior British Association meeting held at Nottingham last July. The Association has arranged lectures for schools and a scientific essay competition is run annually. It has invited overseas students who were in Britain to be its guests at the annual meeting and is hoping shortly to start a science magazine for young people. Industry, which has lately given the Association substantially increased financial support, has been particularly interested in this sort of activity, for it was itself already seeking means of interesting more young people in science and of encouraging them to take up careers in science and technology.

The past year again, saw the delivery at York of the first Kelvin, Lister, and Darwin lectures. These were established to encourage younger scientists (the chosen lecturer must be under thirty-five years of age) to talk about what they are doing, and why, to an audience of intelligent but not technically qualified people. Each of the lectures covers a different group of subjects; the titles of the first three lectures—'Building Viruses', 'Time to React', and 'The Ice Age'—show the breadth of subject.

The popularization of science is not a problem peculiar to Britain, and the British Association has always been aware of what it can learn from, and hope to contribute to, the experience of similar societies in other countries. A necessary task is the organization of conferences on scientific matters of international as well as national importance. The next annual meeting of the Association, at Cardiff, from 31st August to 7th September 1960, will devote a day to World Food Problems—it is striking how many of the overseas groups with which the Association has co-operated have been in Asiatic countries, where a much greater application of science than hitherto is necessary for progress. A two-day conference has been held on the role of science in schools. A committee studying the part played by science in industry is shortly to publish its third report, and a study group to consider the education, in school and university, of the prospective science graduate has also been established. This last group is concerned with a problem which is the reverse of the normal one of the Association: its aim is to investigate how much broadening of the education of science students is desirable, and, if any is desirable, at what stage it should be undertaken. The first year's work has consisted of the study of recent investigations of the educational needs of schoolchildren and the sending out of questionnaires to a selection of university bodies in Great Britain; it is intended also to invite the opinions of professional institutions and industrialists. The Association is also studying another problem involving the co-ordination of a wide variety of interested groups, namely the adoption in Britain of the metric system of weights and measures and a decimal coinage. A committee has been set up to consider the desirability and implications of such a change.

Some, at least, of the aims of the Association are very evidently being achieved by these new activities. The interest of the public, of the national and some foreign newspapers, and of broadcasting and television services has increased—the annual meeting is always extensively reported by informed commentators, and in such a way as to stimulate the public's interest in science. Wider audiences are being reached; the total attendances at meetings organized by Area Committees is now more than ten times the attendance—usually about 3000—at the annual meetings, and they provide an opportunity for contact with a broad section of the public. It is already clear that the recent changes will strengthen the British Association in increasing its traditional role of spreading an understanding and appreciation of science in Britain.

Franz and Ferdinand Bauer, masters of botanical illustration

W. T. STEARN

The work of Franz and Ferdinand Bauer, probably the greatest of all botanical artists, is little known, although there has recently been an exhibition of their illustrations in London. This article describes the background and history of the brothers, and is accompanied by reproductions of some of their drawings, both of plants and of animals.

Modern low-priced reproductions in colour of flower-paintings by Pierre Joseph Redouté (1759–1840), together with the high prices now paid for books he illustrated, have brought him in recent years a fame comparable only with that of his own later years when he 'counted all the prettiest women in Paris among his pupils'; nevertheless he was not unique for his period. Eminent contemporary artists included not only Sydenham Edwards and James Sowerby, but also Franz Andreas Bauer (1758–1840) and Ferdinand Lukas Bauer (1760–1826). These two brothers, the equals of Redouté in their aesthetically satisfying portrayal of general plant-form, stand unrivalled for their accurate and understanding delineation of its finer details; they came nearer to perfection in this field of art and scholarship than any artist before or since. That their achievements are now so little known is probably because their published work is in rare and costly, or very technical, books that are infrequently consulted, while their original drawings lie treasured, but seldom exhibited, in a few institutions, among them the British Museum (Natural History). Here, however, a recent exhibition, arranged by Miss Phyllis Edwards, has given the general public an opportunity of admiring their skill and versatility.

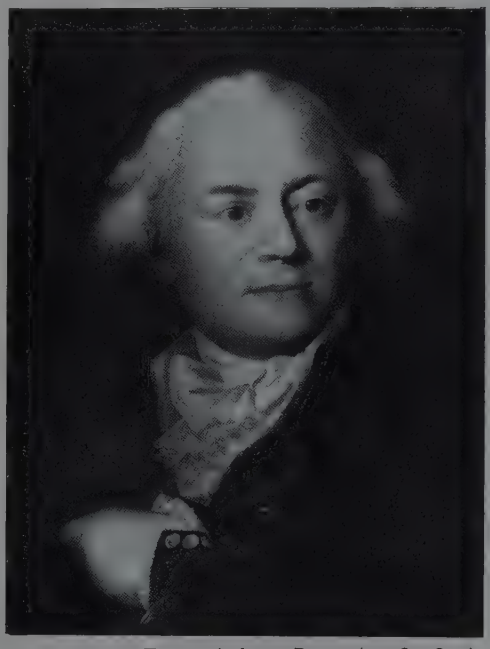


FIGURE 1 – *Franz Andreas Bauer* (1758–1840), *from a portrait at the Royal Botanic Gardens, Kew; artist unknown.*

Conditions in France in the second half of the eighteenth century gave Redouté, who came from Luxembourg, the opportunity to develop his talent under the supervision of noted French botanists and to publish his work there in a sumptuous manner impossible in the land of his birth. In the same way, foreigners provided the Bauer brothers with opportunities far exceeding any then available in their native Austria. They owed these opportunities to a surprising extent to the enterprise and wealth of men of the English landed gentry, possibly the most accomplished and cultured aristocracy the world has ever seen. The supreme representative in science of this British ruling class was Sir Joseph Banks (1743–1820), a great Lincolnshire landowner, and President of the Royal Society from 1778 to 1820. By his persuasion, and at his expense, Franz Bauer settled at Kew in 1790, to paint flowers and investigate their structure for some fifty years. Ferdinand Bauer and Robert Brown sailed in 1801 with Matthew Flinders, under Banks's auspices, to explore the Australian coast (figure 11), as Banks himself and his artist, Sidney Parkinson, had earlier sailed with Cook. Another landed Englishman, John Sibthorp (1758–96), took Ferdinand Bauer on a botanical journey through the Near East and bequeathed an Oxfordshire estate that his flower-portraits might be magnificently

FIGURE 2 – *Koalas* (Phascolarctos cinereus (*Goldfuss*)) *drawn in eastern Australia by Ferdinand Bauer*, 1802–5. (*Original size* $\times \frac{1}{3}$ *approx.*)

FIGURE 3 – *Duck-billed Platypus* (Ornithorhynchus anatinus (*Shaw and Nodder*)), *drawn in eastern Australia by Ferdinand Bauer*, 1802–5. (*Original size* $\times \frac{1}{3}$ *approx.*)

FIGURE 4 – *Indo-Pacific swimming crab, possibly a male of* Portunus trituberculatus (Neptunus trituberculatus *Miers*), *drawn by Ferdinand Bauer, probably in* 1803. (*Original size* × $\frac{2}{3}$.)

FIGURE 5 – Kunzea baxteri (*Klotzsch*) *Schauer* (*Myrtaceae*), *a shrub native to Western Australia, drawn by Ferdinand Bauer, probably in* 1802. (*Original size* $\times \frac{3}{5}$.)

FIGURE 6 – *Details of inflorescence and flower of* Aphyllanthes monspeliensis *L.* (*Liliaceae*), *a xerophytic west Mediterranean species with rushlike stems and the inflorescence reduced to* 1 *to* 3 *flowers within an involucre of brownish bracts, drawn by Franz Bauer.* (*Original size.*)

FIGURE 7 – *Flower of* Stapelia hirsuta *L.* (*Asclepiadaceae*)*; unfinished drawing,* 1804, *by Franz Bauer.* (*Original size* $\times \frac{1}{2}$.)

FIGURE 8 – *Fruits of* Ardisia crenata *Sims* (*Myrsinaceae*), *drawn by Franz Bauer.* (*Original size* $\times \frac{4}{5}$.)

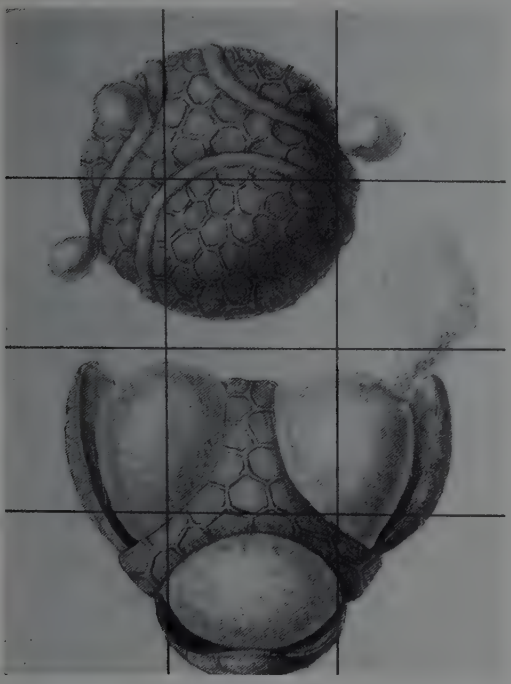


FIGURE 9 – *Pollen grains of* Passiflora quadrangularis *L.* (*Passifloraceae*), *drawn by Franz Bauer.* (*Sides of squares represent* 0·063 *mm*). (*Original size approx.*)

FIGURE 10 – *Flower of* Diuris alba *R. Br.* (*Orchidaceae*), *drawn in eastern Australia by Ferdinand Bauer,* 1802–5. (*Original size* $\times \frac{3}{5}$ *approx.*)

published in the *Flora Graeca*. Lacking such foreign patronage, their brother Joseph Anton Bauer (b. 1756), whose promise in youth was as bright as theirs, achieved nothing comparable.

Their father, Lukas Bauer, after doing religious paintings in Moravia, became court-painter to the Count of Liechtenstein at Feldsberg, Lower Austria; he died in 1761, leaving three sons, Joseph, Franz, and Ferdinand, all born between 1756 and 1760. A local priest, Norbert Boccius, encouraged the orphans in botanical drawing. About 1780 they moved to Vienna and became acquainted with Baron Nikolaus von Jacquin (1727–1817), then engaged in producing a sumptuous folio work, *Icones Plantarum rariorum* (1781–95). By this time, the general adoption of Linnaeus's 'sexual system' of classifying plants, with its emphasis on floral structure, and of his binomial nomenclature for species, which made obsolete so much of the earlier botanical literature, together with the introduction into European gardens of many exotic plants unknown to Linnaeus, had brought about a new era of botanical illustration. Jacquin was now its greatest exponent. Himself a skilled draughtsman as well as an eminent botanist, he quickly appreciated the talent of Franz and Ferdinand Bauer. From him they learned that botanical draughtsmanship is an exacting art which demands understanding of the objects portrayed as well as accuracy and grace in drawing. Under his supervision they became familiar with a diversity of plants, trained their eyes to minute observation, and established their superb techniques. He employed them to illustrate his work, then lost them to Sibthorp and Banks.

In 1786 John Sibthorp of Oxford arrived in Vienna to consult the fifth-century illustrated manuscript of Dioscorides's Greek herbal known as the *Codex Aniciae Iulianae nunc Vindobonensis*. Ancient lore still dominated pharmacy. The usefulness of Greek medical botany was, as E. L. Greene remarked in 1909, 'not only fully realised, but also enthusiastically somewhat over-estimated . . . the greater part of all the new botanical matter published during the whole of the sixteenth century, and a part of the seventeenth, came out in the form of annotations upon the text of Dioscorides'. Sibthorp differed from earlier commentators in going to look for Dioscorides's plants in the region where Dioscorides had lived some 1700 years before. The result was not the retrieving of Greek medical knowledge, as planned, but a modern

FIGURE 11 – *Principal collecting localities in Australia, shown by black dots, of Robert Brown and Ferdinand Bauer, 1801–5. The letters D, J, M, O and T indicate the areas so designated in Brown's* Prodromus Florae Novae Hollandiae (1810): *J, Port Jackson, i.e. from Sydney north to Newcastle, New South Wales; M,* Ora Meridionalis, *i.e. from Cape Leeuwin, Western Australia, east to islands of Bass Strait and Wilson's Promontory, Victoria; T,* Littus intra Tropicum, *i.e. coast of Queensland and Northern Territory west to Arnhem Bay; O,* Ora Occidentalis, *i.e. Western Australia from Cape Leeuwin north to Dampier Land; D,* Insula Van Diemen, *i.e. Tasmania. For further details see* Proc. R. Soc. Queensland, **66** (1), 6–15, 1955; Proc. Linn. Soc. New S. Wales, **80** (3), 229–233, 1956.

botanical work, the *Flora Graeca*, illustrating and describing numerous plants unrecorded by the Ancient Greeks.

Sibthorp engaged Ferdinand Bauer as his artist and the two left Vienna in the spring of 1786, travelled across Italy, by way of Venice, Florence, and Rome, to Naples, and there took ship to Crete. They visited Constantinople, several Aegean islands, Cyprus, and Greece. In December 1787, Sibthorp returned to England, bringing Ferdinand Bauer with him. On this journey Bauer had made about 1000 coloured illustrations of plants, 363 of animals, and 131 of landscapes. Back in Oxford, Sibthorp began to put his notes and specimens in order while Bauer completed his drawings and began to engrave them for reproduction in the proposed *Flora Graeca*. Unfortunately Sibthorp died in 1796 of tuberculosis, with none of his great plans completed, but with adequate provision made under his will for the publication of the *Flora Graeca*. His executors entrusted the work to Sir James E. Smith and, after his death in 1820, to John Lindley. Volume 1 appeared in 1806, volume x (the last) in 1840. Apparently no one connected with the beginning of this monumental task lived to see its end. The cost of the undertaking exceeded £30 000. Only 28 complete sets were originally issued; Henry Bohn made a re-issue between 1845 and 1856 but even that amounted to only 40 copies. Ever important to students of the plants of the Eastern Mediterranean region, this memorial of Sibthorp and Bauer's wanderings and industry is a masterpiece of printing, engraving, colouring, and design, for, without any sacrifice of accuracy, Ferdinand Bauer could make beautiful pictures from the most humble and mean-looking plants. The *Flora Graeca* is the most costly and beautiful book devoted to any flora.

In 1801, Ferdinand Bauer relinquished the unadventurous task of engraving the *Flora Graeca* plates in order to sail to Australia as botanical draughtsman aboard H.M.S. *Investigator* under Flinders (1774–1814). Robert Brown (1773–1858) went as naturalist. Their task was primarily to survey the southern coast of the land then known as New Holland and to discover whether it was a single island or broken into islands by a north-south strait. The *Investigator* sailed from Spithead in July 1801, reached Cape Leeuwin, Western Australia, in December 1801, and Port Jackson, New South Wales, in May 1802. It was no easy voyage. However Flinders, who came of a family of surgeons, and who went to sea largely as a result of reading 'Robinson Crusoe' as a boy, possessed a greater sympathy for natural history investigations than had Cook and Vancouver, and he gave his 'botanic gentlemen' opportunities of landing whenever possible. In Australia they entered a kingdom of strange fantastic plants new to science, for which existing classifications, both natural and artificial, were inadequate. They met its challenge brilliantly. Thus, when the *Investigator* reached Port Jackson, Brown had collected and studied some 750 new species of plants and Bauer had completed about 350 sketches of plants and 100 of animals, although the dampness of their leaky ship injured his drawing paper. After a stay in Port Jackson, Flinders circumnavigated Australia, as he named the island, returning to Port Jackson in June 1803. Here the *Investigator* was condemned as unseaworthy. Flinders, on his way back to England aboard the *Cumberland* to get a new surveying ship, was unjustly imprisoned by the French governor of Mauritius and held captive there for six and a half years. Brown and Bauer fortunately stayed behind in Australia and occupied the next

eighteen months adding to their collections. Brown visited Tasmania, and Bauer spent eight months on Norfolk Island. Their work had far-reaching results. It contributed largely to the end of the artificial Linnaean system of classification in Britain, and laid a sound foundation for future work on the flora of Australia.

In October 1805 they reached Liverpool aboard the repaired *Investigator*. According to a report made by Sir Joseph Banks to the Admiralty, Bauer's sketches numbered 2064, of which 1541 were of Australian plants. They wonderfully supplemented the dried specimens, which included 3900 species. During the voyage Bauer made his sketches 'in such a manner by references to a table of colours [as] to enable him to finish items at his leisure with perfect accuracy'. This he now did. Ten were published later in Flinders's 'Voyage of Terra Australis' (1814) and a few in works by the Austrian botanist Endlicher, but his own *Illustrationes Florae Novae Hollandiae* containing fifteen superb plates of Australian plants was a commercial failure. The first part came out in 1806, the third and last in 1813. Disappointed by the lack of public interest, he returned in 1814 to his native Austria, where he died in 1826.

The career of his brother Franz Bauer was far less eventful. After Ferdinand's departure with Sibthorp, Franz continued working for Jacquin. In 1788 Jacquin's son Joseph went on a tour of European scientific centres, taking Franz with him, obviously to make drawings for Jacquin's works. The facilities for botanical study provided by Sir Joseph Banks's library and herbarium at Soho Square, London, were then unrivalled anywhere. 'When you now have doubt about plants', young Jacquin wrote to his father from London, 'you have only to write to me, for here is the place where one can above all reach certainty'. Banks now controlled the Royal Botanic Garden at Kew and needed a draughtsman to portray its plants. Franz Bauer was obviously his man. In November 1789 young Jacquin wrote, 'Compliments from Bauer. I believe it is high time I brought him away from here, otherwise he will be filched from me. Banks has his eye very much upon him.' He had indeed, and Bauer yielded to Banks's alluring offer. He settled at Kew in 1790 and lived there until his death in 1840. A monument to him adorns St Anne's Church on Kew Green. As stated on this, he was 'Botanical Painter to His Majesty George the Third and Resident Draughtsman for fifty years to the Royal Botanic Garden at Kew. In the delineation of plants he united the accuracy of the profound naturalist with the skill of the accomplished artist to a degree which has only been equalled by his brother Ferdinand. In microscopical drawing he was altogether unrivalled'.

The British Museum (Natural History) possesses many original drawings by Franz Bauer, a large number unfinished. These give the impression that he simply followed his own bent without any direction and purpose except that of satisfying his curiosity and creative urge. He became more and more fascinated by the complicated floral mechanisms of the Asclepiadaceae and Orchidaceae, by pollen grains and spores, and by the histology and anatomy not only of plants but also of animals. Whereas his brother Ferdinand had helped to explore distant lands, discovering and depicting species new to science, Franz patiently explored with lens, microscope, and scalpel the hidden parts of plants around him at Kew, and found in them no less a wealth of material challenging his skill to record graphically and with understanding what few or none had seen before. Unfortunately, from 1810 until 1841, the year in which William J. Hooker took charge, Kew was in decline. Hooker's artist Walter Hood Fitch (1817–92) ultimately enriched botanical literature with some 9960 published drawings. Under such energetic, scientifically minded directors as the Hookers, Bauer's talent would have left a much greater impress upon botany. Nevertheless in his 'Delineations of exotick Plants' (1796–1803), *Strelitzia depicta* (1818), 'Illustrations of orchidaceous Plants' (1830–38), Hooker's *Genera Filicum* (1838–42), and some illustrations in periodicals, he made contributions of very high quality. Both of the brothers were engravers as well as artists, but there seems to be only one published engraving by Franz Bauer, the plate in Stoerck's *Libellus de Usu medico Pulsatillae nigricantis* (1771, reprinted 1907). Plates engraved by Ferdinand adorn the *Flora Graeca*, his own *Illustrationes Florae Novae Hollandiae*, his brother's 'Delineations of exotick Plants', and Lindley's *Digitalium Monographia* (1821).

The great bibliographer Georg August Pritzel in 1872 described Franz Bauer as 'the greatest botanical artist'. It is, however, so often hard to distinguish between his paintings and those of his brother Ferdinand that in fairness one must honour them together as supreme masters of their craft; together they set standards in botanical illustration which have never been surpassed.

Figure 1 reproduced by the courtesy of the Director, Royal Botanic Gardens, Kew; figures 2–10 by courtesy of the Trustees of the British Museum.

Toxic phosphorus and fluorine compounds

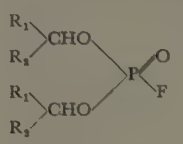
B. C. SAUNDERS

The majority of highly toxic organic compounds containing phosphorus or fluorine were prepared originally, from 1939 onwards, as potential chemical warfare agents. Fortunately they were never used for this purpose, but they proved of great interest, for the investigation of their modes of action has given new insight into some biochemical mechanisms, and suggested valuable uses in clinical medicine and as insecticides. It has also linked up with interesting work on iodine transfer and throws light on the possible functions of iodine in the blood. Research on these compounds and their methods of action is reviewed in this article.

Before 1939, compounds of the types discussed below had received little attention, and few practicable methods of preparation had been recorded. The compounds then examined were of two main types: (*a*) phosphorofluoridates, containing the P—F link; (*b*) fluoroacetates, containing the C—F link.

PHOSPHOROFLUORIDATES

Early in the war a series of dialkyl phosphorofluoridates (I) was synthesized [1]. It was found



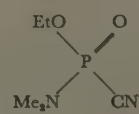
I

that these substances could be produced in excellent yield from cheap and accessible materials [2], and we investigated their effects on animals and on ourselves, and on enzyme systems. A most interesting member of the series, synthesised in 1941, was diisopropyl phosphorofluoridate (DFP) in which $R_1 = R_2 = CH_3$. When we exposed ourselves to DFP at a concentration of $1 : 10^6$ for five minutes, practically no effects were noted during exposure nor until some five minutes later. Intense myosis, that is, extreme pupil constriction, and reduction of the powers of accommodation, then set in and often persisted for seven days, with little relaxation of symptoms in less than 72 hours. At higher concentrations the toxicity[1] was such as to cause a quick knock-out action in animals. The L.C. 50 was 0·36 mg/l for rats and 0·44 mg/l for mice; the symptoms were muscular cramps, gasping, and finally cessation of respiration. This means that DFP is more toxic than chloropicrin and comparable with hydrogen cyanide.

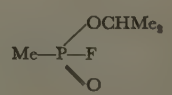
Investigations on the relationship between physiological effects and chemical constitution showed that the more potent compounds are derived from secondary alcohols [3]: thus the diisopropyl derivative is more potent than the di-n-propyl phosphorofluoridate, and the toxicity of dicyclohexyl phosphorofluoridate is high (L.C. 50 for mice, rats, and rabbits is 0·11 mg/l). Again, di-n-butyl phosphorofluoridate is weakly toxic and produces only feeble myosis, whereas the di-sec-butyl derivative ($R_1 = CH_3$, $R_2 = C_2H_5$) is comparable with DFP.

We showed that in substances of the type $(RO)_2POX$, toxicity is high if X is fluorine, but that the myotic effect is absent and toxicity low if, for example, $X = H$, C_2H_5, OH, OC_2H_5, OCH_2CH_2Cl, Cl, NH_2, or $NHCH_3$. Toxicity is also low in the aromatic series (for example, diphenyl phosphorofluoridate), and the difluoridate $(C_2H_5O)POF_2$ was inactive [4].

In further experiments, a large range of phosphorodiamidic fluorides [5], such as $(CH_3NH)_2POF$ was prepared, many of which were found to be toxic, but to have no myotic action. 'Hybrid' compounds, of the type $(RO)(R_1NH)POF$, were found to be highly toxic: these closely resemble the German 'G agents', tabun (II) and sarin (III) which are highly toxic and produce marked myosis.



II



III

[1] Toxicity by inhalation (L.C. 50) is here expressed as the concentration in mg/l required to kill 50 per cent of the animals after 10 minutes' exposure.

THE MECHANISM OF POISONING BY PHOSPHOROFLUORIDATES

The action of phosphorofluoridates on enzymes was first investigated in Cambridge in 1941, and it was shown that they inhibit the action of cholinesterase, which hydrolyses acetylcholine [6]. The diisopropyl derivative is active against the enzyme in extremely low concentrations (about 10^{-9}M against 'pseudo' cholinesterase and about 10^{-7}M against 'true' cholinesterase[1]). This effect was shown not to be due to fluoride ion, which might be produced by hydrolysis, as sodium fluoride required a high concentration (10^{-2}M) to give 50 per cent inhibition of cholinesterase activity; the same molar concentration of ammonium phosphorofluoridate was necessary for 50 per cent inhibition. Eserine, known for a long time as a strong inhibitor of cholinesterase, requires a concentration of 10^{-8}M; moreover its action is easily reversible, whereas that of DFP is not. Radioactive-tracer methods showed that one molecule of DFP combines with approximately one molecule of enzyme, producing complete inactivation.

We will now consider the possible significance of these results, and describe, in general terms, what appears to happen at the junction of a mammalian motor nerve-fibre and a striated (voluntary) muscle. On stimulating the nerve, acetylcholine ($Me_3N^+CH_2CH_2OCOCH_3$), is liberated, as represented diagrammatically in figure 1. The acetylcholine then alights on 'receptor' patches within

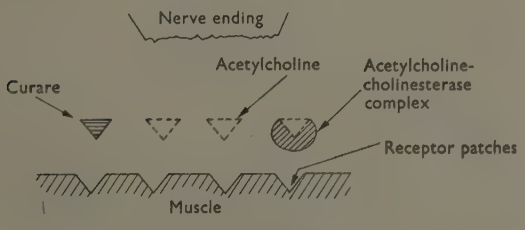


FIGURE 1

the muscle, which it may be assumed can exactly accommodate it, causing contraction. Subsequently cholinesterase converts acetylcholine into choline, which does not fit the receptor patches and is therefore inactive, and acetic acid:

$$Me_3N^+CH_2CH_2OCOCH_3 + H_2O = Me_3N^+CH_2CH_2OH + CH_3COOH.$$

The contraction of the muscle thus ceases. A complex is undoubtedly first formed between the enzyme and acetylcholine, and this presumably does not fit the receptor patches. Curare, which paralyses motor end-plates, presumably also fits into the receptor patches and thereby excludes entry of acetylcholine: curare itself, however, has no direct action on muscle. Thus a nerve gas which inhibits cholinesterase causes acetylcholine to accumulate, and therefore, among other actions, would be expected to cause intense contraction of striated muscle. In this respect the effect of acetylcholine resembles that of nicotine.

The autonomic nervous system activates smooth muscle, cardiac muscle, and glands: it thus governs functions that usually do not obtrude upon consciousness. It has two divisions, sympathetic and parasympathetic, with complementary or antagonistic actions. Thus stimulation of the parasympathetic system causes the pupils to contract, and also causes constriction of the bronchioles, slowing of the heart, constriction of the lumen of the gut, etc. [8]. Stimulation of the sympathetic system has the opposite effect (figure 2). Acetylcholine is liberated at the ends of parasympathetic

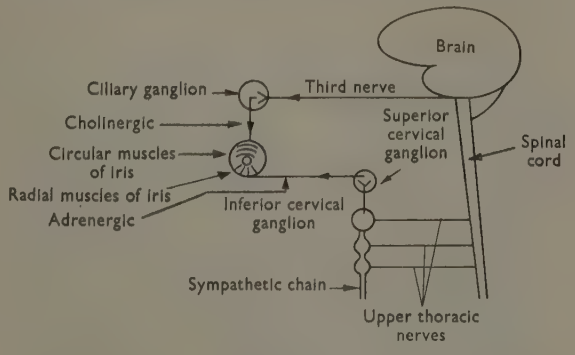


FIGURE 2

fibres, whereas adrenalin or noradrenalin is liberated at the ends of sympathetic fibres [9]. Thus, a nerve gas which inhibits cholinesterase potentiates parasympathetic activity and so is known as a parasympathomimetic agent. When the reinforcement of parasympathetic activity is sufficiently great, the animal dies. The effects of acetylcholine on the autonomic nervous system are shown in figure 3. It should be noted that acetylcholine is also liberated at the synapse between the pre- and post-ganglionic fibres of all autonomic nerves. Thus with severe poisoning the whole nervous system is thrown into chaos. The action on striated muscle is, as mentioned, similar to that of nicotine, whereas the action on a

[1] Broadly speaking, 'true' cholinesterase occurs in erythrocytes and brain and 'pseudo' cholinesterase in serum [7].

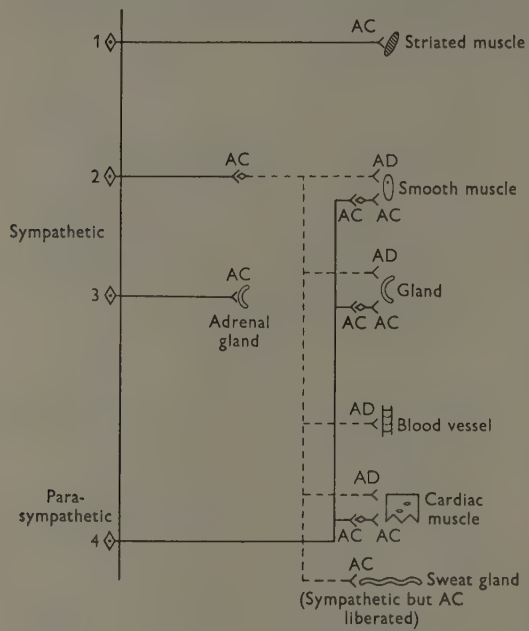
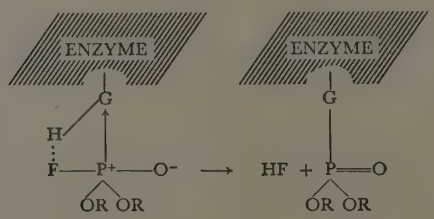


FIGURE 3

post-ganglionic parasympathetic fibre resembles that of muscarine.

Besides compounds of the type $(RO)_2POX$ in which X represents fluorine, toxicity and anticholinesterase activity are observed when X represents an anhydride structure, for example tetra-alkyl pyrophosphates and *p*-nitrophenyl esters. Nevertheless, the fluorine atom in such compounds cannot be replaced by other halogens without loss of toxicity. Hence the fluorine atom must have some property, such as the formation of a hydrogen bond [8] between the fluorine atom and a hydrogen atom of the enzyme (IV), that enables it to



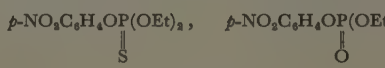
IV

complex readily with cholinesterase. Such hydrogen-bond formation is not likely with the phosphorochloridate, but certain other phosphate esters containing oxygen, nitrogen, or sulphur might well participate in such bonding. Very recent theories advanced by other workers also indicate hydrogen bonding [10].

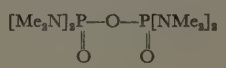
APPLICATIONS

The applications of compounds of this nature fall into two groups, clinical uses, and uses as insecticides and fungicides. Thus, the condition of post-operative paralytic ileus (paralysis of peristaltic movement of the gut) appears to be relieved to some extent by intramuscular injection of DFP and other organophosphorus compounds. Again, transient relief of symptoms of myasthenia, in which too little acetylcholine or too much cholinesterase may be produced, has been recorded. DFP has also been suggested for treatment of glaucoma caused by increased intraocular pressure, by direct administration of an oily solution to the affected eye. It seems that DFP facilitates the escape of the aqueous humour from the eye.

As mentioned above, while this work on phosphorus and fluorine was proceeding in England during the war, German workers pursued projects similar in some respects. Among compounds recommended by G. Schrader [11] as insecticides are

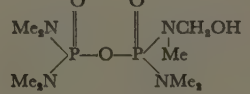


and tetraethyl pyrophosphate. For example, the systemic insecticide Shradan (V), first prepared by Schrader, has been used to control aphids on hops.



V

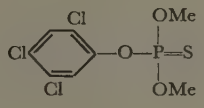
As stated, there is often a correlation between anticholinesterase activity *in vitro* and mammalian toxicity. However, Shradan is not much less toxic than DFP and yet its anticholinesterase activity *in vitro* is negligible. This is accounted for by its conversion by living tissue (for example liver) into a different substance (VI) which is the real toxic material, with cholinesterase-inhibiting properties: hence it has a delayed action [12].



VI

Several other 'inactive' organophosphorus compounds are changed to toxic materials by animal and plant tissue, that is, the tissue is capable of lethal synthesis.

An interesting compound, trolene (VII), of low



VII

mammalian toxicity, deals effectively with the cattle grub, which is the larval stage of the heel or warble fly [13]. The fly hatches out in the spring and lays its eggs on cattle, the usual site being the short hairs on the legs of the animal. The eggs hatch and the larvae burrow under the animal's skin and cut breathing holes through the hide. Trolene previously administered to the animal kills the migrating grubs within its system before they can cause damage.

FLUOROACETATES

Apart from early work by F. Swarts [14], these compounds attracted little attention before the war. Methyl fluoroacetate, a mobile liquid with an extremely faint odour, was the first compound to be investigated in detail [15]. Animals did not usually exhibit any symptoms during exposure to lethal concentrations of the vapour, and no obvious effects were noted for 30–60 minutes after exposure. Convulsions then took place and death usually followed within a few hours. For rabbits and guinea pigs, the L.C. 50 was about 0·1 mg/l: mice were rather more resistant. Intravenous injection produced symptoms similar to those displayed after exposure to the vapour, and even with large doses a delayed action was observed. The L.D. 50 for rabbits[1] was about 0·25 mg/kg.

In the phosphorofluoridate series, the intensity of toxic action varies with the alcohol grouping, whereas the toxicities of fluoroacetic acid, and of ethyl, n-propyl, and iso-propyl fluoroacetates are similar to that of methyl fluoroacetate. On the other hand, methyl α-fluoropropionate (Me.CHF.COOMe) and methyl α-fluoroisobutyrate, ($Me_2CF.COOMe$) show negligible toxicity: it is important to note that these compounds do not contain the FCH_2CO– group.

[1] Toxicity by injection (L.D. 50) is expressed as the dose in mg/kg body weight required to kill 50 per cent of the animals.

Again, when the acyl halides, fluoroacetyl chloride (FCH_2COCl), chloroacetyl fluoride ($ClCH_2COF$), and fluoroacetyl fluoride (FCH_2COF) were examined it became obvious that toxicity depended upon the FCH_2CO– group, whereas —COF was ineffective. Further confirmation was provided by the observation that ethylfluoroformate (FCOOEt), also containing the —COF group, was non-toxic.

Fluoroacetamide, FCH_2CONH_2, and numerous substitution products of the type FCH_2CONHR were convulsant poisons with delayed action. The magnitude of their toxicities suggested that they were hydrolysed to fluoroacetic acid in the animal body.

There is a striking alternation [16] in the toxic properties of ω-fluorocarboxylic esters:

FCH_2COOR (toxic)
$F(CH_2)_2COOR$ (non-toxic)
$F(CH_2)_3COOR$ (toxic)
$F(CH_2)_4COOR$ (non-toxic)
$F(CH_2)_5COOR$ (toxic)
$F(CH_2)_7COOR$ (toxic)
$F(CH_2)_{10}COOR$ (non-toxic)

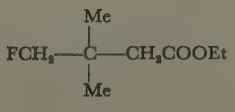
Other series of fluorine compounds showing alternation in toxic properties are also known.

F. Knoop suggested in 1906 that fatty acids were metabolised in the body with loss of two carbon atoms at a time by oxidation at the β-carbon atom

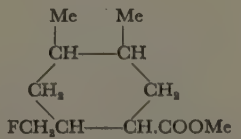
$$RCH_2CH_2COOH \longrightarrow R.COOH + CH_3COOH$$

[17]. It will be readily seen that in the series $F(CH_2)_nCOOH$, when n is odd, β-oxidation must be expected to yield toxic fluoroacetic acid, whereas when n is even, the compound will be oxidized only to the non-toxic β-fluoropropionic acid. The results are in accord with this hypothesis and provide new evidence of the process of β-oxidation of fatty acids in the living animal body.

If this interpretation is right, then blocking of the β-position to prevent oxidation should give a compound devoid of toxic properties. For this purpose ethyl 2 : 2-dimethyl-3-fluorobutyrate (VIII) was synthesised, and shown to be non-toxic



VIII



IX

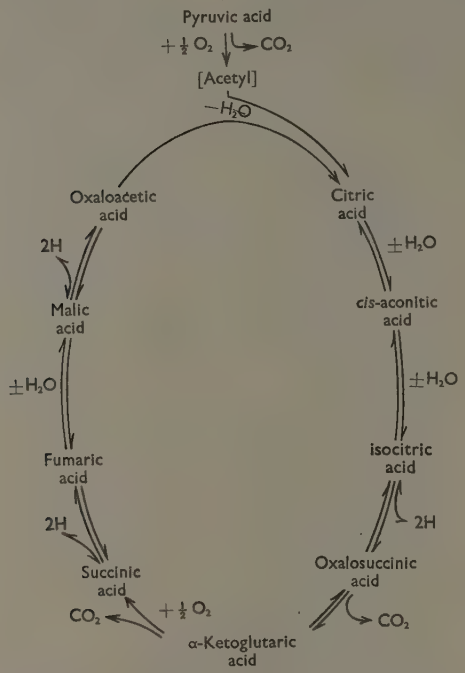
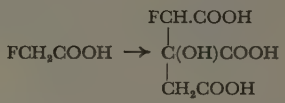


FIGURE 4 – *Principal reactions in the Krebs cycle.*

[18]. Another way of testing the theory was to incorporate the β-carbon atom in a carbon-ring so that the body could not oxidize the compound to fluoroacetic acid. Accordingly the compound (IX) was synthesised, and again found to be non-toxic.

MECHANISM OF FLUOROACETATE POISONING

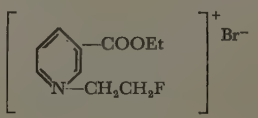
R. A. Peters and his colleagues have shown that poisoning by fluoroacetate is brought about by blocking the 'tricarboxylic acid cycle' (figure 4), and have proved that fluoroacetate is converted to fluorocitrate [19]. The enzyme aconitase, which



occurs within the mitochondria, is concerned with the conversion of *cis*-aconitate to either citric acid or isocitric acid. Peters suggests that there is competition for aconitase between fluorocitrate and citrate, and hence accumulation of citric acid should result from fluoroacetate poisoning. This is found to be so. In short, fluoroacetate poisoning results from the conversion by enzymes *in vivo*. This is a good example of the synthesis *in vivo* of a lethal substance from a less toxic (or non-toxic) substance, a phenomenon that has already been mentioned in connection with phosphorus esters.

M. B. Chenoweth [20] has demonstrated the protective effect against fluoroacetate poisoning by certain compounds such as glycerol monoacetate: this may be explained as being due to interference with the conversion of fluoroacetate to fluorocitrate.

A compound that can be metabolized readily to fluoroacetic acid will enter the tricarboxylic acid cycle and be converted to toxic fluorocitric acid. Thus fluoroethanol, fluoroacetaldehyde, and fluoroacetamide are equally toxic [21]. Quaternary salts (X) are non-toxic. This is understandable, as



X

they are unlikely to undergo easy conversion to fluoroacetic acid. It is surprising, however, that sodium fluoropyruvate is much less toxic than fluoroacetic acid: this indicates that no fluoroacetyl fragment is formed from fluoropyruvate.

TABLE I

Results of Transiodination Reactions [26]

Iodine donor	Iodine acceptor	Transiodinated product
4-Iodo-2:6-dimethylaniline	*p*-Hydroxyphenylacetic acid	3:5-Diiodo-4-hydroxyphenylacetic acid
4-Iodo-2:6-dimethylphenol	Tyrosine	Mono- and di-iodotyrosines
Diiodotyrosine	Thyronine	3'-Iodothyronine
Diiodotyrosine	3:5-Diiodothyronine	Thyroxine
3-Iodotyrosine	3-Iodotyrosine	3:5-Diiodotyrosine

The explanation seems to be that fluoropyruvate alkylates thiol compounds, and thus that the actions of coenzyme A and 6 : 8-thioctic acid, which control the entry of pyruvate into the citric acid cycle, are inhibited [22].

RECENT WORK ON COMPOUNDS CONTAINING THE C-F LINK

Recent work by Belgian investigators is of considerable interest [23]. It is well known that cells are damaged by X-rays and γ-rays, and it appears that, following radiation, the deoxyribonucleic acid of the cell nucleus is destroyed by the enzyme deoxyribonuclease which occurs in mitochondria. This reaction requires the presence of magnesium ions. The Belgian workers have established that previous injections of sodium fluoroacetate into mice give some protection against irradiation: this may be due to the fact that fluoroacetate causes accumulation of citrate ions which combine with, and so remove, magnesium ions.

The physiological action of certain compounds is altered when hydrogen is replaced by fluorine. American workers claim that monofluoro derivatives of steroid hormones are more potent than the parent substances: thus 6-α-fluoroprogesterone is ten times as active as progesterone [24]. Again, 6-α-fluorohydrocortisone acetate has eleven times the activity of hydrocortisone.

PHOSPHORYLATION AND TRANSIODINATION

Recently, research on iodine transfer in the body has, somewhat surprisingly, linked up with that on phosphorus compounds. We have shown [25] that peroxidase converts *p*-iodoaniline into 2-amino-5-*p*-iodoanilinobenzoquinone, di-*p*-chloranil, and tetra-*p*-iodoazophenine. This took place with the facile removal from *p*-iodoaniline of the stable iodine atom as the iodide ion: the latter was then oxidized completely to I_2, the process being accelerated by peroxidase. The iodine immediately reacted with iodoaniline to give 2 : 4-diiodoaniline, an example of de-iodination followed by re-iodination. The reaction has now been extended so that a compound other than the original substrate becomes the iodine acceptor. Thus the peroxidase system is able to effect a process that one may call transiodination.

Reactions involving this intermolecular transfer of iodine under the influence of peroxidase were then investigated, attention being paid to compounds similar to those present in the thyroid gland. Some results are shown in Table 1.

The investigation was then extended to other

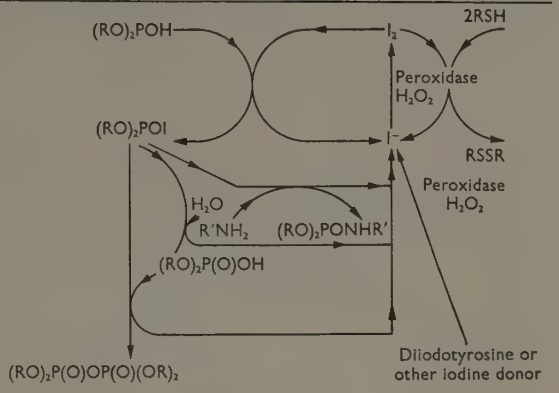


FIGURE 5

reactions in which peroxidase systems, in the presence of iodine, might be utilized. Quantitative yields of phosphoroiodidates had previously been obtained by the action of iodine on trialkyl phosphites:

$$(RO)_3P + I_2 = (RO)_2POI + RI$$

However, when dialkyl hydrogen phosphites were used in place of trialkyl phosphites, the reaction was almost entirely suppressed. It was clear that the hydrogen iodide first formed interfered in some way with the formation of phosphoroiodidate. It seemed then that, if the reaction between iodine (or an iodine-donor) and a dialkyl phosphite could be carried out in the presence of peroxidase, a high yield of the phosphoroiodidate should result. This has indeed been found to be so.

$$(RO)_2POH + I_2 \xrightarrow{\text{peroxidase}} (RO)_2POI + HI$$

Since phosphoroiodidates react with amines to give dialkyl phosphoramidates and iodide, it was thought worth while to investigate the formation of P-N bonds in the presence of the enzyme. Such a system did in fact give good yields of phosphoramidate.

It is known that the controlled hydrolysis of phosphoroiodidates yields tetra-alkyl pyrophosphates and iodide, and it was found that the enzyme system could be used in the formation of P—O—P links. In the accompanying scheme (figure 5) a cyclic formation and oxidation of iodide continually occurs; thus the peroxidase system is able to bring about the formation of phosphates, pyrophosphates, and phosphoramidates in the presence of only catalytic amounts of iodine.

The formation of disulphide linkages from —SH groups by the action of peroxidase and iodine has also been studied. Here again, hydrogen iodide is

formed, oxidized, and returned to an earlier part of the cycle as iodine:

$$2RSH + I_2 = R—S—S—R + 2HI$$

Thus cysteine was readily converted to cystine by peroxidase and hydrogen peroxide, in the presence of diiodotyrosine as iodine donor.

It is known that some 8 μg of iodine are present in 100 ml of systemic blood, and this work may serve to indicate possible functions for it. In this connection, peroxidase can serve three purposes: (i) release of iodine from an iodine-donor, (ii) actual transfer of iodine—'transiodination', (iii) oxidation of iodide to iodine, ensuring the circulation of iodine. All these processes are represented in figure 5.

It may be that some of the substances used in the phosphorylations are somewhat artificial, nevertheless they represent certain new general principles, which are capable of extension to materials of more biological significance.

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The nonulosaminic acids—complexes of carbohydrates and amino acids

M. STACEY

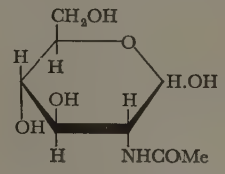
Since Blix first obtained crystalline bovine 'sialic' acid in 1936, substances of the same class, chemically remarkable as being hybrids of sugars and amino acids, have been isolated from a very wide range of mucoproteins present in animal tissues and body fluids. The chemical nature and inter-relationships of these substances, now known as nonulosaminic acids, have been established, and there is growing evidence of their great biological importance, especially in the defence mechanisms of the body, which is discussed in this article.

AMINOSUGARS

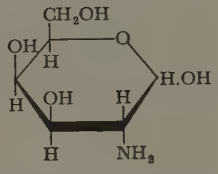
In recent years there has been a growing recognition of the biological significance of the nitrogen-containing sugars, or aminosugars, which form important constituents of animal, insect, and bacterial tissues and of body fluids. They constitute a large part of the building units of those highly complex macromolecules—composed of polysaccharides and proteins, and fats—known respectively as mucopolysaccharides, mucoproteins, and mucolipids.

In the animal body, these mucosubstances form skeletal material, connective tissues, cell membranes, mucinous lubricating substances, and so on. They have various functions, such as those of protective and connective agents, and often they are present as viscous secretions having an association with movement within the body. Thus we have the serum mucoids in blood movement; urinary mucoids in water and ion movement; joint, ocular, and skin mucoids in anatomical and muscular movement; and salivary, gastric, and intestinal mucins in digestive movement. With the macromolecules are present, usually, the enzymes that build them up and break them down. All these substances play an important role in health and disease, in injury, in reproduction and growth processes, and so on. Of particular importance are the mucosubstances of the eye, the complex heparin which is the anticlotting substance of the blood, and the many substances contributing to the viscosity of blood plasma.

In insects, crustacea, and micro-organisms the mucosubstances form skeletal material and thus have, in particular, a protective function. Chitin (I), the 2-acetamino-2-deoxy derivative of cellulose, is one of the most stable organic substances known in nature and plays a role in insects and crustacea analogous to that of cellulose in plants.

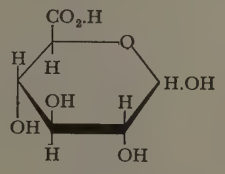


I. N-acetyl-D-glucosamine, of which chitin is a polymer

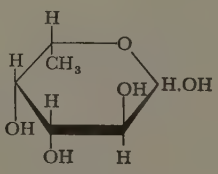


II. 2-amino-2-deoxy-D-galactose

Another commonly occurring simple aminosugar is that commonly known as galactosamine or chondrosamine (II) which is an important constituent of cartilaginous tissue, especially in young animals.



III. D-glucuronic acid



IV. 6-Deoxy-hexose (L-fucose)

Early work in the field was reviewed in 1925 by P. A. Levene [1], an outstanding pioneer in the field of complex molecules. Numerous efforts at naming the substances and various classifications [2] have been attempted and the whole subject has recently been discussed from the biological aspect [3].

In a complex macromolecule, the aminosugars are frequently associated with the common hexoses, D-glucose and D-galactose, and also with 6-carboxy and 6-deoxy hexoses (III and IV). Specific biological tests—such as blood group specificity, prevention of blood clotting, enzymatic activity—are often available to test the purity of a mucosubstance or of an enzyme which builds it up or breaks it down. Physical and

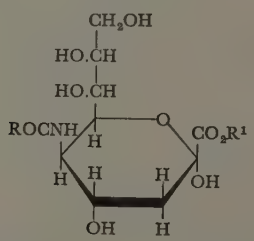
chemical tests, often applicable on a micro- or a histochemical scale, are available to locate and estimate the simple building units of the complex molecules.

A striking colour reaction is given when 2-amino-2-deoxy sugars are first condensed in alkali with acetylacetone or acetoacetic ester to form pyrrole-type compounds, which are then allowed to react with Ehrlich's reagent (*p*-dimethylamino-benzaldehyde). The chemistry of this reaction is complex but it can be adapted [4] to give quantitative estimation of substances such as glucosamine and, by further modification, of acyl derivatives also.

With some aminosugar derivatives, it is possible by preliminary treatment with alkali to obtain a colour reaction without the addition of acetylacetone. This has been called the 'direct Ehrlich reaction'; the study of its complexities has been most fruitful and in particular has led to the discovery of the acids here reviewed.

NONULOSAMINIC ('SIALIC') ACIDS

Most of the mucosubstances, especially mucoproteins, give the direct Ehrlich reaction, and search for the substances causing the reaction has led to the discovery that combined with most of the mucoproteins and the mucolipids is a remarkable group of '9-carbon' sugars—first described under such names as 'sialic', 'neuraminic acids'—which can be classed as nonulosaminic acids (v) [5].



v. General structure of nonulosaminic acid

Members of the group have been crystallized (figure 2) and derivatives have been synthesized. Remarkable pioneer work on the sialic acids has been carried out over a period of more than thirty years by G. Blix of Uppsala, who in 1936 succeeded [6] in crystallizing the 'B-sialic acid' he had obtained from bovine submaxillary-gland mucin. Outstanding work in another field, namely that of certain fatty substances of the brain (known as the 'gangliosides') has been carried out, again over many years, by E. Klenk of Cologne. In 1941 [7] he crystallized 'neuraminic acid' which subsequently Blix and his colleagues [8] pointed out was a de-acetylated derivative of sialic acid.

The precise relationships between the sialic acids, neuraminic acids, and other natural aminosugar complexes have now been established. Notable contributions to the more recent studies have been made by, among others, A. Gottschalk from Australia, Richard Kuhn from Germany, L. Svennerholm from Sweden, and F. Zilliken from the United States. The acids possess nine or more carbon atoms and have a molecular composition typified by $C_{11}H_{19}NO_9$, O-sialic acid (ovine). They possess a carbonyl group, an amino group, a carboxyl group, frequently an acyl group (such as methoxyl, acetyl, or glycolyl), and they can exist, in one case at least, in polymeric form.

The nonulosaminic acids are very labile to acids (a property characteristic of 2-deoxy sugars) and also to alkalis, harsh treatment converting them to the intractable substance humin. This lability hindered their early investigation and called for considerable patience on the part of the pioneer investigators.

They can readily be recognized by the brilliant red colour formed directly on addition to them of an acid solution of the Ehrlich reagent. They give a bright purple colour on being boiled with Bial's reagent (orcinol) while the Dische reagent for deoxypentoses (diphenylamine in acetic and sulphuric acids) gives with the acids a vivid blue-violet coloration. Paper chromatography is most useful for separating and identifying the acids (figure 1). Since crystalline standard substances have now become available, quantitative estimation of the amount of the acid in various animal tissues has become of great interest.

NOMENCLATURE

There has been much confusion in the literature concerning nomenclature. From time to time acids from different sources, but obviously related to the known sialic acids of Blix, were characterized, for example, the lactaminic acid of cow colostrum (R. Kuhn) and gynaminic acid of human milk (Zilliken and Gyorgy).

Blix named his sialic acids according to their origin, for example P-sialic acid (porcine), O-sialic acid (ovine), E-sialic acid (equine). Eventually, G. Blix, E. Klenk, and A. Gottschalk [10], the principal workers in the field, agreed that the parent acid (not yet crystallized) should be termed neuraminic acid, while the name, sialic acid, should denote its various mono- and di-acyl derivatives, regardless of their origin. Neuraminic

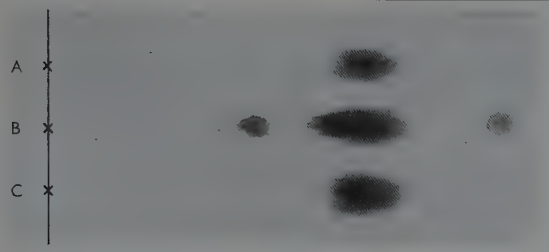


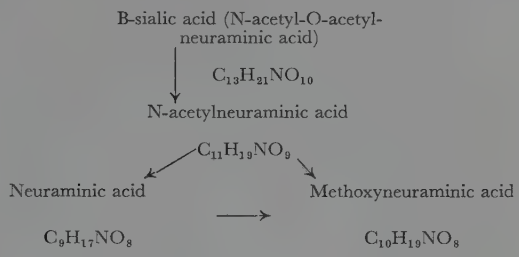
FIGURE 1 – *Chromatographic behaviour of neuraminic acid.* (A) *N-acetylneuraminic acid from human serum.* (B) *a mixture of N,O-diacetyl-, N-acetyl-, and N-glycolyl-neuraminic acids isolated from chronic-bronchitis sputum.* (C) *N-acetylneuraminic acid from submaxillary mucin.*

acid may be described as 5-amino-3 : 5-dideoxy-D-erythro-L-gulu-nonulosonic acid [9]. F. Zilliken and M. W. Whitehouse [5] and W. J. Whelan [9] have set down the inter-relationships between the acids in various tables.

STRUCTURE AND SYNTHESIS

Difficulties of crystallization and analysis led to many discrepancies and about a dozen formulae in turn were suggested, but improved techniques of purification, and the separation of crystalline substances, at last gave an insight into the relationships between the different acids. Brilliant studies in the laboratories of Blix, Klenk, Gottschalk, Zilliken, and Kuhn led to the present accepted formula, first proposed by Gottschalk. The standard of reference for investigation has been Blix's sialic acid.

The empirical relationships are as follows:



Their very similar colour reactions with Ehrlich's and Bial's reagents and their interconversions by acylation and deacetylation established the relationship between the acids. N. Hiyama [11] in 1948 showed that acid hydrolysis of submaxillary sialoproteins yielded 2-pyrrole carboxylic acid and this acid was obtained by Gottschalk in 1954 from the interaction of influenza virus and urinary sialoprotein. Later it was obtained from N-acetylneuraminic acid.

In 1955, Blix [12] provided evidence regarding the five hydroxyl groups in his B-sialic acid and also identified an N-acetyl and an O-acetyl residue. Further work showed that the acid could arise from an aldol condensation product of N-acetyl-D-glucosamine and pyruvic acid.

A synthesis [13] has been achieved by allowing N-acetyl glucosamine to react slowly with oxalacetic acid ($CO_2H—CO—CH_2—CO_2H$) and from the mixture of condensation products N-acetyl

TABLE 1

Synonyms of neuraminic acid and its derivatives
(*Whelan* [9])

	Molecular formula	Synonyms
Neuraminic acid	$C_9H_{17}O_8N$	Prehemataminic acid
Methyl neuraminosidic acid	$C_{10}H_{19}O_8N$	Methoxyneuraminic acid Hemataminic acid
5-N-Acetylneuraminic acid	$C_{11}H_{19}O_9N$	O-sialic acid (ovine) Gynaminic acid Lactaminic acid Serolactaminic acid
Methyl 5-N-acetylneuraminidate	$C_{12}H_{21}O_9N$	Methoxylactaminic acid
5-N-Acetyl-7-O-acetylneuraminic acid	$C_{13}H_{21}O_{10}N$	B-sialic acid (bovine)
5-N-Acetyl-?-O-acetylneuraminic acid	$C_{13}H_{21}O_{10}N$	E-sialic acid (equine)
5-N-Glycolylneuraminic acid	$C_{11}H_{19}O_{10}N$	P-sialic acid (porcine)

neuraminic acid was isolated in low yield. However, the acute observation was made by S. Comb and D. G. Roseman [14] that the aminosugar component of the acid, which was split off by an enzyme 'neuraminidase', was N-acetyl mannosamine. They have now achieved the synthesis of N-acetylneuraminic acid from synthetic N-acetyl-D-mannosamine and pyruvic acid. Mannosamine and glucosamine are very readily interconverted.

OCCURRENCE OF NONULOSAMINIC ACIDS

In the native state the acids all occur associated with other macromolecules such as proteins, fats, and polysaccharides, and must first be liberated either by autolysis or by mild hydrolysis at room temperature. They are very soluble in water but they can readily be selectively adsorbed out of aqueous solutions by means of ion-exchange resins. From the resins the nitrogen-substituted acids can be separately eluted by means of acetic or formic acids. Serum, milk, colostrum, cerebrospinal fluids, and erythrocytes are particularly good sources.

Fatty complexes. Brain material contains important neuraminic acid complexes, especially in the gangliosides which are abundant in the ganglion cells of the nervous system. The gangliosides are sphingolipids of the following general structure:

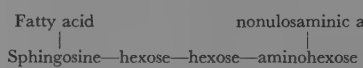
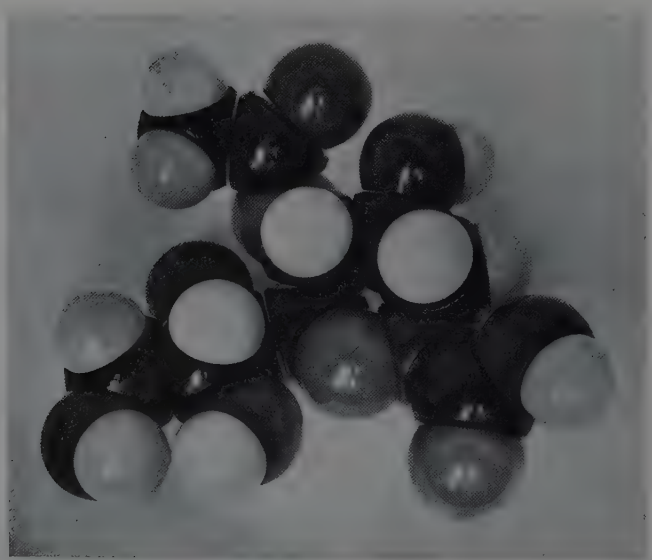


FIGURE 2 – *Crystals of N-acetylneuraminic acid. (Isolated by M. Z. Atassi, Chemistry Department, Birmingham University.)*



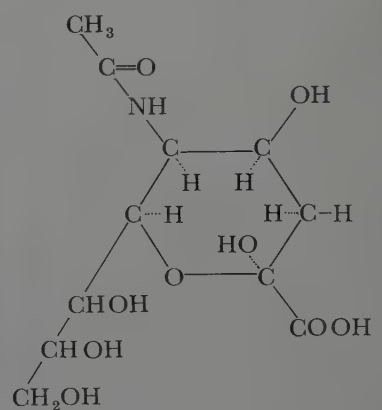


FIGURE 3 (*left*) – *N-acetylneuraminic acid. Visible groups (those within the ring are not seen) are as indicated in the above formula.*

In certain fatty disorders in humans, for example, lipidoses, there is an unusual accumulation of gangliosides and hence of nonulosaminic acids: the detailed structure of various gangliosides is being studied in special cases. Some acids are present to the extent of 25 per cent in other complexes known as cerebrosides.

Protein complexes. In the viscosity-producing substances of the body is a group of 'sialoproteins' which contain significant quantities of nonulosaminic acid. This class of protein is widely distributed in body fluids, for example in saliva, vitreous humour, urine, bronchial and epithelial tissue, gastro-intestinal and genital tracts, cysts, cerebrospinal fluids, milk (especially colostrum), serum, liver, brain, and erythrocytes.

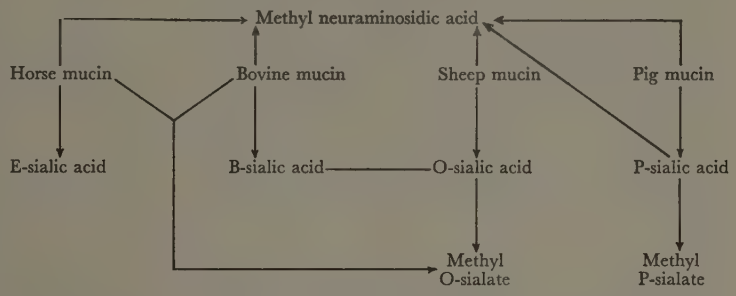
The carbohydrate fractions invariably contain D-mannose, L-fucose (IV), D-glucosamine, D-galactosamine, and D-galactose. Submaxillary glands have been widely used by Blix and his colleagues as a source of their sialic acids. The structures of these vary slightly according to the source: for example N-acetylneuraminic acid from human saliva, milk, brain, and serum, and N-glycolylneuraminic acid from pig submaxillary mucin.

In serum, it appears that the acid is present only in the globulin proteins; the particular γ-globulin that has the highest content (10 per cent) is termed orosomucoid. The normal content of the acids in human serum is surprisingly high, for example 65 mg per 100 ml. In certain diseases the concentration may be raised considerably, but the significance of the increase is not known. In animals such as mice, the concentrations may be as high as 90 mg per ml.

Colominic acid, a remarkable polymer of N-acetylneuraminic acid, has been isolated from culture filtrates of *E. coli* [15].

TABLE II

Inter-relationships of sialic acids from submaxillary-gland mucins (From Whelan [9])



INDIVIDUAL ACIDS

Sialic acid. Blix and his colleagues have paid particular attention to the isolation and purification of bovine and equine sialic acids, which have been identified as N-acetyl-O-acetyl derivatives. To obtain them, the mucinous content of epithelial tissues was extracted with cold water, and the solids were precipitated by addition of solvents. The precipitate was boiled with water, the extracts were evaporated to dryness, and the residue was extracted gently with methyl alcohol. The acid was made to crystallize from the alcoholic solution by addition of ether and petroleum.

While preparations from different sources were not identical—having different melting points, optical rotations, and other physical properties—they all gave rise to N-acetylneuraminic acid. The differences are considered to be due to the O-acetyl group taking up different positions around the sugar ring.

Methoxyneuraminic acid. This compound ($R^1 = CH_3$, minus N-acetyl in V) is the most stable, and most easily accessible, derivative of a nonulosaminic acid. It has been isolated directly in crystalline form from, for example, erythrocytes, liver, milk, and serum protein. It was originally isolated by Klenk from brain gangliosides, which gave a high yield of a crystalline acid melting at 200° C.

N-acetylneuraminic acid. This was probably obtained first as a by-product in the previous preparation, though it is now known that its methyl ester had previously been obtained under the name of methoxy lactaminic acid from bovine colostrum. In addition the free acid ($R^1 = H$, $R = CH_3$ in V) had been obtained from human milk and termed gynaminic acid. Crystallizations (figure 2) from aqueous acetic acid gave alkyl-free acids and revealed that ovine-sialic, lactaminic, and gynaminic acids were all N-acetylneuraminic acid, a model of which is shown in figure 3. Infrared studies and X-ray diffraction patterns have been valuable in this work.

More recent methods of preparation have involved the boiling of oligosaccharides, obtained from such sources as submaxillary mucin and meconium by treatment with 0·001N sulphuric acid at 70° for 60 minutes. Even more recently the tissue

materials have been acted on by neuraminidases in order to liberate the N-acetyl derivative.

N-Glycolylneuraminic acid. In the hands of Blix and his associates, pig submaxillary mucin has yielded a most interesting acid ($R^1 = H$, R = glycolyl in v) known as N-glycolylneuraminic acid (melting point 186–187°, $[\alpha]_D - 31°$). It also occurs in various gangliosides and in sialoprotein from erythrocytes of other animals. The glycolic acid residue can be split off by acidic hydrolysis. Doubtless other derivatives of nonulosaminic acids will in due course be found to be naturally occurring.

THE NATURE OF NONULOSAMINIC ACIDS AND THE BLOOD CELL RECEPTOR FOR INFLUENZA VIRUS

G. K. Hirst [16] in 1942 made the startling discovery that influenza virus caused a clumping (haemagglutination) of red blood cells of chicks. He showed that this involved an interaction between the virus particles and the surface components of the red cells. This phenomenon in the chick cells was thought to be the beginning of the process of infection, even though other cells which were not susceptible to infection had surface components which reacted with virus. The whole interaction was shown by Hirst to be part of, or very similar to, an enzymic reaction, the receptor red cell surface being the 'substrate' and the combined virus the 'enzyme'. The virus, in a state still capable of causing further infection, could be eluted from the red cells: the latter, however, could no longer be agglutinated with a fresh sample of virus, and thus had become changed in some way.

It was established that the process of elution of the virus was connected with the removal of receptor substances from the red-cell surface. Then it was found that the haemagglutinating action of the virus could be inhibited if the virus was first treated with a substance of carbohydrate nature similar in structure to the components of the red-cell surface. A rich source of such inhibitors was found in a range of heat-stable sialoproteins present in normal sera.

The capacity of the sialoproteins to inhibit haemagglutination is rapidly lost on incubating them with the virus, and this loss of activity is accompanied by the release of a 'split product' from the protein. The cause of the loss of activity due to a 'receptor-destroying enzyme', and the split product which gave the direct Ehrlich colour reaction, have been identified, through the work of Gottschalk, and of Klenk and his co-workers, as N-acetylneuraminic acid, which has been found in all the mucoprotein inhibitors so far tested. Preliminary work shows that both the protein moiety and the nonulosaminic acid in the sialoproteins are necessary for inhibitory capacity. It is interesting that not all the nonulosaminic acid is released by this enzyme and that the amount of released material is not a measure of inhibitory power.

There is some evidence that nonulosaminic acid forms a terminal group in some sialoproteins, particularly in ovomucin, submaxillary mucin, and urinary mucin. In bovine submaxillary mucin, Gottschalk has shown that the sialic acid is labile to both acid and alkali and it is probably bound by a glycosidic linkage. He therefore termed the viral enzyme a neuraminidase, indicating that it splits off a glycosidically-linked neuraminic acid. These virus enzymes are now being intensively studied and bacterial sources of some of them, for example *Vibrio cholerae*, have been found. A neuraminidase which liberates a nonulosaminic acid from the α acid globulin, orosomucoid, has been obtained from *Clostridium perfringens*.

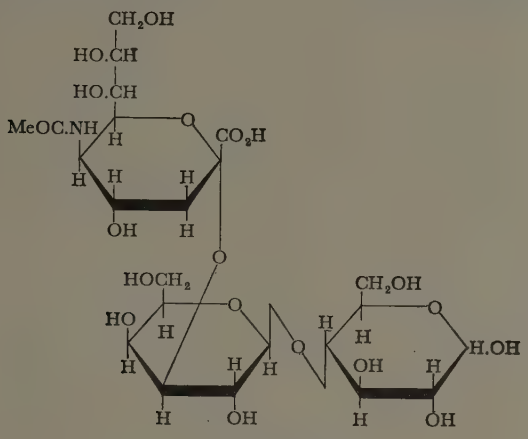
OLIGOSACCHARIDES CONTAINING NONULOSAMINIC ACID

Much work has been done on the oligosaccharides of milk. The non-dialysable fraction of human milk contains various neutral aminosugars and two acidic oligosaccharides which yield L-fucose, D-glucose, D-galactose, N-acetyl-D-glucosamine, and N-acetylneuraminic acid.

The smaller dialysable carbohydrate fraction may contain as many as five nonulosaminic acid oligosaccharides, one of which has been termed neuraminolactose. From a study of the methyl ether and its degradation products, R. Kuhn and K. Brossmer [17] deduced the structure (VI) for the trisaccharide: its N-acetyl derivative was isolated from cow's colostrum. The action of neuraminidase liberated N-acetylneuraminic acid and its glycosidic linkage with the lactose was located at the third carbon atom of the D-galactose residue, as shown. Gottschalk [18] has recently studied a disaccharide obtained from bovine salivary mucoprotein and has discovered that it contains N-acetylneuraminic acid and N-acetyl-D-galactosamine.

BIOLOGICAL IMPORTANCE OF NONULOSAMINIC ACIDS

The study of these interesting compounds has



VI. N-acetylneuraminolactose

not yet reached the stage at which their biological importance can be fully assessed: their wide occurrence was unsuspected even a few years ago. There is no doubt of the biological importance of complexes of polysaccharides and proteins, and the existence of a series of crystalline compounds which are a cross between simple sugars and aminoacids must offer exciting biochemical prospects. The fact that different animals yield different nonulosaminic acids is of great interest and may be important from a diagnostic point of view.

The connection of the N-acetyl compound with virus attack on red cells may prove to be of great importance. It already seems clear that, with influenza virus at least, the virus attaches itself to part of the nonulosaminic acid pattern at the cell surface. It then produces an enzyme which detaches the neuraminic acid from the host cell, thereby liberating itself so that it is free to pass on and attack another cell in order to continue its metabolic cycle. The occurrence of colominic acid in *E. coli* must cause speculation as to whether bacteriophage attack can be studied in this way; certainly nonulosaminic complexes formed at cell surfaces will well repay investigation.

Important studies are being made by S. Bogoch [19] on the significance of neuraminic acids and on the chemistry of gangliosides in certain brain disorders. With S. A. Barker and other colleagues, we are studying the mucoproteins containing neuraminic acid in a variety of abnormal tissue fluids such as tumour tissues and bronchial mucin. The nature and quantitative amounts of the acids present in these may well prove to be of high significance.

The feeling pervading all this work is that these acids somehow play a vital role in defence mechanisms of the human body. The fact that they are so frequently present as end residues at the chain-ends of the big mucoprotein molecules provides a means of investigating more precisely their biochemistry.

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Book reviews

NUCLEAR THEORY

Introductory Nuclear Theory, *by L. R. B. Elton. Pp. xi+286. Sir Isaac Pitman & Sons Ltd, London.* 1959. 40*s. net.*

This book is an introduction to the main facts of nuclear physics from a theoretical viewpoint, and it should be valuable either to the research student who is just beginning to work on the subject or to the general scientific reader. The background knowledge which the reader requires at the beginning is not great—the Schrödinger equation, Maxwell theory, and the simplest ideas of special relativity are sufficient. More advanced theoretical methods are then developed as they are needed. Among these are the separation of the centre of mass and the relative motion in the two-body Schrödinger equation, the phase shift expansion for the elastic scattering amplitude, Dirac's relativistic electron equation, and the formulae for the electromagnetic multipole matrix elements. The level of mathematical technique required is everywhere kept as low as possible.

The main topics discussed are: binding and stability, elastic scattering and the nucleon-nucleon potential, isotopic spin, nuclear models (degenerate gas, shell model, liquid drop, etc.), reactions and the Breit-Wigner formula, β- and γ-ray emission, photodisintegration and radiative capture, and the elements of the meson theory of nuclear forces.

With such a wide range of material and techniques to be covered in a book of modest size, it is not to be expected that the treatment can be very deep or that it will be smooth throughout. Nevertheless Dr. Elton is to be congratulated on doing a good job. The main ideas of elementary nuclear physics have been put across clearly and adequately, and no important topic has been omitted. At the end there is a useful table of nuclear data and a list of references for further reading.

J. HAMILTON

ELECTROCHEMISTRY

The Structure of Electrolytic Solutions, *edited by W. J. Hamer. Pp. xii+441. John Wiley and Sons Inc., New York; Chapman and Hall Ltd, London.* £7 8*s. net.*

A study of the published proceedings of symposia sometimes prompts the thought that both travel and publication have become too easy. This is emphatically not the case with this volume which is a stimulating and useful collection of papers based on those presented at a symposium held in Washington in May, 1957; it is a pity that it has taken so long for the volume to appear, but it may be that the quality of some papers has been enhanced by the opportunity thereby afforded to authors for reflection after the conference.

The title accurately reflects the deeper insights now being obtained into the molecular nature of electrolyte solutions both by more refined analysis of conventional properties and by the application of new techniques. The range of topics covered is wide: Raman spectral investigations of ionic equilibria, proton solvation and transfer, diffusion processes, the ion-species present in aqueous ammonia, ion solvation, methods of determining acidity constants, ion association, the properties of rare-earth salts, melts, and the measurement and interpretation of general thermodynamic properties are all discussed. The book can be recommended both to the expert and to any who think that all the worthwhile problems in the field were solved three decades ago. Unfortunately the price is very high indeed.

J. E. PRUE

ELECTROPHORESIS

Electrophoresis—Theory, Methods and Applications, *edited by M. Bier. Pp. xx+563. Academic Press Inc., New York; Academic Books Ltd, London.* 1959. $15.00.

As Professor Tiselius says in his foreword, 'The development of electrophoretic methods and their application form an unusually beautiful example of the fruitfulness in the application of physical methods to biochemical and biological problems' and this book, which is a collaborative effort, is a timely recognition of the need for an authoritative work dealing fully with the theoretical and practical aspects of this important subject. It is not a manual of laboratory procedures, these being included only for illustrative purposes. The aim is much wider, the emphasis being on the principles and broad applications of the methods discussed. The first two chapters deal with the electric potentials in colloidal systems and with acid-base equilibria of proteins. Then follow sections on the theory and practice of moving-boundary electrophoresis, electrophoresis in systems stabilized by paper and other supporting materials, and finally preparative and analytical applications of the various methods, including chapters on clinical and physiological applications, and studies on viruses, bacteria, and cells. The exposition is of a uniformly high standard throughout, whilst the illustrations and diagrams are clear and relevant to the text. This book can be thoroughly recommended both to those already familiar with the subject and to those who wish to understand the principles underlying these fascinating techniques and to consider how they might be applied with advantage to their own problems.

A. J. WOIWOD

TRANSURANIUM ELEMENTS

The Transuranium Elements, *by G. T. Seaborg. Pp. xx+328. Yale University Press, New Haven, Connecticut; Methuen & Co. Ltd, London.* 1958. 50*s. net.*

This is a most unusual and interesting book. It is based on the four Silliman lectures delivered by G. T. Seaborg at Yale in May, 1957, and can be described, perhaps, as a scientific autobiography.

The first part, the plutonium story, contains the most accurate and detailed account published of the chemical investigations with which the author was associated in the Manhattan Project, and subsequently in the American Atomic Energy Commission. No one is in a better position to relate this story, and the account loses none of the dramatic qualities of the events themselves.

The second part reviews our present knowledge of the chemical properties of these elements and of their relation to their neighbours. The considerably larger third section deals with the nuclear properties of the isotopes of these elements, and the part they have played in extending our knowledge of nuclear forces and of the nature of the fission processes, as well as the methods of prediction of the nuclear characteristics of new isotopes. The last, and shortest, part contains some interesting speculations on the possibility of the discovery of new transuranic elements.

The second and third sections summarize the contributions of the author

and his Californian research school to nuclear science. It is now possible to see these achievements in perspective and to assess their importance to chemistry and nuclear physics. They have had remarkable repercussions in both of these fields and it would indeed be difficult to judge which were more important. In this book one can find the history of science in the making.

A. G. MADDOCK

HETEROCYCLIC CHEMISTRY

Heterocyclic Chemistry, *by A. Albert. Pp. viii+424. The Athlone Press, University of London, London.* 1959. 45*s. net.*

Heterocyclic chemistry can no longer be presented as a series of syntheses, of melting points and boiling points, and of smells. Literature surveys and recent research have amassed a wealth of information, but it lacks perspective, and to encompass it in a single volume requires a new approach. This, by his book, Professor Albert seeks to supply. He does not ignore syntheses nor the interest of natural products, but his dominant theme is the fundamental and comparative behaviour of the ring systems.

He divides the subject into hetero-paraffinics, hetero-ethylenics, and hetero-aromatics. The last is the main class and is subdivided according as the carbons of the ring have a deficiency of π-electrons (pyridine, its benzologues and azalogues) or an excess (azoles, furane, thiophen). This provides a rational basis for discussing properties both within and between groups of heterocycles, and, on the framework erected, ionization constants, spectra, reduction potentials, and dipole moments figure prominently, as do addition and substitution reactions, and substituent reactivity. As supplements to each group discussion, important individual compounds are briefly described.

This book is opportunely conceived, lucidly written, and well documented. It will appeal to students and teachers, to specialists and non-specialists alike.

J. D. LOUDON

EVOLUTION

Darwin and the General Reader, *by Alvar Ellegård. Pp.* 393. *Gothenburg Studies in English, Gothenburg.* 1958. 28 *Sw. Kr.*

Dr Ellegård has performed the heavy task of finding, studying, and classifying the reviews of Darwin's *Origin of Species* and *Descent of Man* that appeared in the British daily, weekly, monthly and quarterly press during the dozen years that followed publication of the first edition of the *Origin*. By this means the author has made available material on which to study the interest which Darwin's works and theories kindled among the general public, and the treatment the works received at the hands of the reviewers at that time. Darwin himself counted 265 reviews of the *Origin*, excluding those which appeared in 'newspapers.'

The first impression gained on reading Dr Ellegård's book is one of astonishment at the high seriousness with which supernatural and miraculous interpositions of divine power into the order of nature were admitted by men of science, who apparently failed to realize that the order of nature was thereby made disorderly.

Secondly, when these opinions are added to those of the theologians, their sum made such a preponderance of hostile, sarcastic, and misinformed criticism of evolution and natural selection, that it is a matter for wonder that Darwin's views ever made any headway at all.

Thirdly, it is striking to see the number of journals and newspapers which then published reviews of such books as a matter of course. The majority of these journals are now defunct. A comparison with present conditions is depressing, for when the new series of exhibits illustrating the proofs of evolution by natural selection was opened in the Natural History Museum in London in celebration of the Darwin-Wallace centenary in 1958, only one newspaper devoted as much as half a column to the event. The author has provided an invaluable yardstick with which to measure progress in the history and dissemination of some of the most important ideas in the world.

GAVIN DE BEER

MICROBIOLOGY

Recent Progress in Microbiology, *edited by G. Tunevall. Pp.* 453. *Blackwell Scientific Publications, Oxford.* 1959. 70*s. net.*

This book records the six symposia of the seventh International Congress of Microbiology, held at Stockholm in 1958. It embraces topics which may appear at first sight to have little in common. Nevertheless, a sense of unity is derived from the book as a whole. Symposia on the response and tolerance of the body to its own antigens, on the rearing and experimental use of germ-free animals, and on latent virus infections illustrate the extensive growth of connecting channels between the study of micro-organisms and that of other forms of life. Several symposia are concerned, in one way or another, with the synthesis and interrelationship of nucleic acid and protein. They pass from the techniques and terminology of genetics to biochemical experiments with intact cells, cellular fragments, and isolated enzymes, and describe exciting advances, some doubtless less permanent than others, in fields of the widest biological interest. Most of the authors have themselves made notable contributions to the work they describe. Although some of the ground is covered in other recent reviews, major fragments of this book should be found stimulating by a large circle of biologists and biochemists.

E. P. ABRAHAM

MOLECULAR BIOLOGY

Symposia of the Society for Experimental Biology, *No. XII.* The Biological Replication of Macromolecules, *edited by F. K. Sanders. Pp. vi+255. Cambridge University Press, London.* 1958. 50*s. net.*

This volume is a worthy successor to its eleven predecessors in the series, and affords an interesting comparison with the first symposium, that on nucleic acids, held in 1947; at that time the structure of the nucleic acids had not been fully established. The present volume shows how stimulating has been the full determination of this structure and the realization that its duplex and complementary form suggests a molecular basis for the self-copying ability which must underlie all genetic mechanisms. It is therefore not surprising that nearly half the papers of this symposium refer to some aspect of the structures and biological roles of deoxyribonucleic acid and nucleoproteins. However, some of the most interesting work reported is in the more well-established fields of protein and of polysaccharide biosynthesis. The concluding papers extend the scope even further into discussions of the processes co-ordinating intracellular activity and the use of tissue transplantation in the study of cellular heredity. Not the least interesting aspect of the symposium is the interplay it reveals between widely disparate studies. Clearly work in this field demands a range of knowledge and understanding on the part of the individual

investigator which our traditional divisions of the sciences are ill-equipped to provide.

The volume is a stimulating progress report on one of the most significant fields in which the various sciences are co-operating. Its deficiencies arise from the nature of all such reports of symposia. Not only can a symposium rarely assemble all the potentially useful contributors, but the proliferation of reports of this kind increases considerably the difficulty of the average investigator in attempting to read the literature in his field of interest. What are the respective functions of the ordinary journals and of reports of symposia? Too often there is considerable overlap, and the same material is reported in both types of publication. This merely renders confusion worse confounded, although in the present instance both the quality of the papers and their modest number makes the volume of considerable interest and usefulness. A. R. PEACOCKE

CYTOGENETICS

Cytology and Cytogenetics, *by C. P. Swanson. Pp. x+596. Macmillan & Co., London.* 1958. 45*s. net.*

Chromosomes have attracted close study ever since their first clear identification over eighty years ago, and the knowledge that has been gained, constituting the subject of cytogenetics has become an intricate, sophisticated, and provocative system of ideas. This is Swanson's sphere of interest, and he handles his material with accomplished ease and balance, sorting the often forbidding detail with a simple logic. His chief concern is with the dynamic; the greater part of the book has to do with the behaviour of chromosomes and the evolution of chromosomal systems, in both plant and animal kingdoms, and these topics are treated systematically and with impressive thoroughness. A possible criticism is that the author's point of view reflects a specialist's preoccupation with his own field—the parent science of cytology, prominent in name in both title and text, is developed only as an introduction, albeit a most adequate introduction, to the main theme of cytogenetics. Subjects of special interest to the reviewer which receive scant or no attention from Swanson include the cytological origins of heteroploidy, regulation to diploidy, pre- and post-reduction, and sex chromatin.

Swanson's book will be invaluable to formal geneticists requiring a cytological background, to students wishing to specialize in cytogenetics, and to the general biologist as a reference book on chromosomes. It is commendably low priced for its size and wealth of illustration. There are rather more than 1000 references, those of American origin predominating. C. R. AUSTIN

PLANT GROWTH SUBSTANCES

Plant Growth Substances, *by L. J. Audus. Pp. xxii+553. Leonard Hill (Books) Ltd, London.* 1959. 65*s. net.*

Anyone who has attempted a survey of a small section of the field of plant growth substances will have nothing but admiration for this book. Professor Audus has continued to cover the whole of this vast subject with its seemingly interminable ramifications in a way that is both understandable and thought-provoking. It is six years since the first edition was published, and the flow of scientific papers has continued unabated. The increase in price of the present volume is more than justified by its contents, for the author has not been carried away by the flood but has succeeded in keeping abreast.

There is a noticeable expansion of the chemical sections to keep pace with more recent findings and a very valuable chapter devoted to the mechanism of the action of the auxins has been introduced. The academic research worker will find all the available information (including a sixty-four-page bibliography) critically displayed for him; that the applied branches of the subject (for example, herbicides) are equally adequately covered means that this excellent book will have a wide appeal. The thirty-six pages of appendices give practical information of great use to the grower.

W. G. TEMPLEMAN

BOTANY

Circumpolar Arctic Flora, *by Nicholas Polunin. Pp. xxviii+514. Clarendon Press, Oxford.* 1959. £6 6*s. net.*

The Arctic has been described as a hovel for plant life. The winter is long, dark, and intensely cold, the summer is short, most of the subsoil is frozen the whole year round, and the precipitation is low. Nevertheless 230 genera of the north temperate zone have managed to produce low-growing species hardy enough to survive in the wastes beyond the northern tree limit. Most genera there have less than 6 species but *Carex* reaches 67, *Salix* 40, and *Saxifraga* and *Antennaria* 24, according to the assessments in this book. This is the first taxonomic account of the whole arctic vascular flora which has ever been completed. Since many species found in the Arctic proper also occur elsewhere, for example in Scotland and the Alps, the work has also an interest for students of the temperate flora in general. It provides keys, descriptive notes and line-drawings for the 892 species accepted by the author, whose concepts are admittedly broad, on the ground that 'an extraordinarily high proportion of arctic plants "run into" each other so intricately, in one or another part of their world range . . . that it is often exceedingly difficult to know where in the maze of available phases one species stops, morphologically speaking, and the next begins'. There is little documentation, infraspecific taxa are not distinguished, specimens are rarely cited, and geographical distribution even within the Arctic is indicated only in general terms. These would be serious dificiencies in a critical flora. The author's aim is, however, simply to provide a counterpart for the Arctic of Bentham and Hooker's *Handbook of the British Flora* and in this he has well succeeded. Every accepted species is illustrated; although the illustrations vary greatly in style and precision—crude outlines appear discordantly side by side with exquisitely delicate portraits—they all effectively show the habit of growth.

W. T. STEARN

ENDOCRINOLOGY

Memoirs of the Society for Endocrinology, *No.* 6. Implantation of Ova, *edited by P. Eckstein. Pp. vii+97. Cambridge University Press, London.* 1959. 30*s. net.*

This book gives the proceedings of a conference held at the Ciba Foundation, London, in November, 1957, under the chairmanship of Sir Solly Zuckerman. It is particularly fortunate that not only the papers but also the discussions which followed them have been fully recorded here. We are still largely ignorant of the factors that control how, when, and where mammalian embryos implant in the uterus, but in this book one can readily grasp the main lines along which research is developing. The contributors include anatomists, endocrinologists, and a biochemist, each an expert who, at this conference, was specially concerned to make his viewpoint clear to listeners outside his own field, so that we enjoy

here a clarity of exposition that would seldom be met with in an ordinary text-book. A helpful introductory review by Eckstein, Shelesnyak, and Amoroso outlines the several approaches, which are then taken up individually by later speakers. Some of the problems they deal with are: why implantation is delayed for so long in badgers; what is the significance of the rich glycogen secretion in human uterine glands; what is imbibed, besides water, by the rabbit blastocyst before it implants; how implantation may be artificially delayed or speeded by hormone administration; and whether there is any limit to the number of embryos that may implant in the mouse. A proper balance is kept between descriptive and experimental work, and all is put clearly into perspective by the critical discussions. E. M. DEUCHAR

NORTH-AMERICAN ZOOGEOGRAPHY

Zoogeography, *edited by C. L. Hubbs.* Symposium presented on 26–27th August, 1957, at the joint meeting of the American Institute of Biological Sciences and the Pacific Division of the American Association for the Advancement of Science, Stanford, and a Symposium presented on 28th December, 1957, at the Meeting of the American Association for the Advancement of Science, Indianapolis. *Pp.* x+509. *Bailey Bros. & Swinfen Ltd, London.* 1958. £5 8*s. net.*

Almost the only thing wrong with this excellent symposium is the title; it is not devoted to zoogeography in general, but entirely to that of North America. But within these limits, nearly every aspect of zoogeography is dealt with. Particularly welcome are a geologist's summary of the development of the great montane areas of western North America, and a physiologist's review of the distribution of terrestrial vertebrates. Also notable are a discussion of climate in North America since the Cretaceous, and a well-written survey of the Pleistocene ecology and biogeography of North America. These provide background studies against which the rest of the papers can be read; they are surveys of the zoogeography of mammals, birds, reptiles and amphibia, fishes, various insect-groups, and a few other invertebrates. No account is given of quite a number of invertebrate groups, which is not surprising, but regrettable. The papers on groups vary greatly in approach; some authors are quite positive about the exact phylogeny of all their forms, some equally certain about the exact place of origin of each group, others vague about both. A close study of the fifteen papers published in full in this volume can be recommended to every zoogeographer. A. J. CAIN

MARINE BIOLOGY

The Open Sea, *Part* II, Fish and Fisheries, *by Sir Alister Hardy. Pp. xiv*+322. *Collins, London.* 1959. 30*s. net.*

Public concern for the living resources of the sea has been heightened in recent years by the series of unfortunate (and, some think, unnecessary) fishing disputes, with their attendant special pleading. One must, therefore, welcome Sir Alister Hardy's book as a contribution to the spreading of accurate knowledge, untainted by politics and vested interests, of life in the sea. Although it can be read by itself, it is also a natural sequel to his volume on plankton in the same series. The book starts with chapters on fish in general, and brings the reader quite logically to an account of the fauna of the sea floor, which include not only bottom-living fishes, but a multiplicity of invertebrate animals—crustaceans, molluscs, echinoderms, and many others—which play an important part in the economy of the sea. The result is a brilliant synthesis of knowledge of the sea and its fisheries, based on the most recent research, and with no space wasted on unconfirmed fishing tales and the longshore bric-a-brac which mars so much writing in the field of marine natural history. The author has spent his life in the service of the sea, with his mind turned to its fauna as a living world, in which the environment is more important than an exact knowledge, essential though it is, of the number of rays in a cod's dorsal fin. The result is a book full of information presented in lively style.

The chapters on marine reptiles and on whales and other marine mammals are particularly valuable. The book is illustrated by the author's own water-colour and line drawings, delightful in their freshness, and by excellent black and white photographs, many of them by Dr Douglas Wilson, the doyen of marine natural history photography.

H. G. VEVERS

NORTH-AMERICAN ZOOLOGY

The Mammals of North America, *Vols. I and II, by E. R. Hall and K. R. Kelson. Vol. I, pp. xxx*+546+79; *Vol. II, pp. viii*+547–1083+79. *The Ronald Press Company, New York.* 1959. $35.00 *the two volumes.*

The appearance of this monumental study will be a thrill for all those who are interested in the mammalian fauna of North America. For a resident in Britain, where there are so few mammals, the first reaction must be one of envy of those who live in a country with such an enormous variety of these animals.

Here are recorded the physical characteristics, habits, and distribution of 1003 species. Incidentally, the number is less than has been recorded from this area by many previous workers, a sign of the most careful pruning of doubtful and subspecific groups that has been adopted. The description of each species is accompanied by drawings of the skull and a map of the distribution.

It is not for one inexpert in the systematics of the area to criticize the detailed attributions. The production is excellent, with an extensive bibliography and index. J. Z. YOUNG

INSECTICIDES

DDT—The Insecticide Dichlorodiphenyltrichloroethane and its Significance, *edited by P. Müller; Vol. II,* Human and Veterinary Medicine, *edited by S. W. Simmons. Pp.* 570. *Birkhäuser Verlag, Basle.* 1959. *Fcs.* 66.

This volume is the second of the trio planned as a comprehensive treatise on the insecticide DDT. In the present volume W. J. Hayes, S. W. Simmons, and E. F. Knipling respectively review the pharmacology and toxicology of DDT, and the problem of residues in food, its use in human medicine by the control of insect vectors, including a section on the problem of insect resistance to DDT, and the use of DDT in veterinary medicine. These contributions represent the most exhaustive survey of the relevant literature yet to appear and contain some 1500 separate references. There is remarkably little overlap between the sections and all reflect industry, care, and the authority of the authors. One difficulty in any work of this magnitude is to keep abreast of contemporary developments. For example, with one exception, there are no references to literature published later than 1954. This is of significance to the field under review because the problem of insect resistance has certainly affected the relative values of the various insecticides during the last five

years. Finally one might question the usefulness of a work devoted solely to DDT which, despite its great historical significance, remains only one of several very powerful and important insecticides. Nevertheless, on account of their authority and comprehensive nature, all three volumes should appear on the shelves of the scientific and technical reference libraries.

F. P. W. WINTERINGHAM

COLOUR VISION

Visual Problems of Colour. A Symposium held at the National Physical Laboratory, September 1957. *Pp.* 368. *H.M. Stationery Office, London.* 1958. 42*s. net.*

The proceedings of this symposium make an interesting comparison with those of a similar conference held in Cambridge ten years earlier at which Professor Selig Hecht had played a dominant part. Appropriately, the conference opened with the Selig Hecht Memorial Lecture, delivered by Professor George Wald on 'Retinal Chemistry and the Physiology of Vision'. It provides a magnificent synopsis of the advances made in those aspects of the subject which were at the very centre of Hecht's interests.

Of the other contributions, nearly forty in all, it is probably fair to say that those which display the most remarkable advances are concerned with the physiology of colour vision. The demonstration of the spectral sensitivities and of the bleaching of the cone pigments in the human fovea, and the recent results obtained by localized electrical recording in the retinae of various animals provide fundamentally new data.

The conference was very broadly international, and several papers from Soviet scientists are included.

E. N. WILLMER

MATERIALS RESEARCH

Molecular Science and Molecular Engineering, *by A. R. von Hippel. Pp.* xv+446. *Technology Press of M.I.T. and John Wiley & Sons Inc., New York; Chapman and Hall Ltd, London.* 1959. £7 8*s. net.*

This book is an attempt to survey some of the fundamental properties of matter in a way which will interest all scientists, and especially engineers.

Professor von Hippel is assisted in this volume by a number of distinguished contributors, and the result is a fascinating mixture of short essays on a wide variety of topics. An outline of atomic and molecular structure (27 pages) is followed by an account of electrical conductivity and breakdown in gases (20 pages) and of thunderstorms (10 pages). This leads on to microwave breakdown in gases (10 pages), to an account of gaseous discharges as technical devices (14 pages), and to a short outline of explosions in gaseous systems.

The final part of the work is concerned with electrical and magnetic properties, especially with ferroelectric, anti-ferroelectric, and ferromagnetic materials. The last three chapters are on polyelectrolytes, on ion-exchange resins, and on rectifiers and transistors.

The author has made an heroic effort to attain a useful synthesis of sciences in this book, but it is hardly surprising that many features should be unsatisfactory. The articles are rather uneven in quality, and many of them are almost inevitably either rather superficial or so condensed as to be almost incomprehensible without much further reading. Although no one could expect to obtain a satisfactory insight into any of these topics from this book alone, a reader already well acquainted with some of them will find much to interest and stimulate him.

R. E. RICHARDS

INDUSTRIAL MEDICINE

Industrial Hygiene and Toxicology, *Vol. I,* General Principles (*second revised edition*), *edited by F. A. Patty. Pp. xxviii*+830. *Interscience Publishers Inc., New York.* 1958. $17.50.

Interest must be aroused by a statement on the pre-title page that the new edition of this work is to be expanded to three volumes. Interest in the facts and practical guidance to be included in the other volumes should, however, not detract from the value of Volume I.

Much of the subject matter has been revised and brought up to date. The changes follow the trend of American thought expressed in the relevant literature of recent years. The sections on factors in fatigue and competence are replaced by sections covering safety in engineering and industry, industrial sanitation, heat control, and industrial noise and lighting problems, In view of the interest aroused by two recent conferences in Britain the sections on noise and lighting should be of great value. They set out simply the theory and then enlarge on the practical aspect of these problems. Also of current and growing interest is the revised section on radiant energy.

With this advancement it is a pity that the section 'Sampling and Analysis of Atmospheric Contaminants' remains almost unchanged. It is to be hoped that reference to the developments over the last ten years will appear in the projected third volume, 'Industrial Environmental Analysis'.

W. M. DIGGLE

HISTORY OF SCIENCE

A Short History of Scientific Ideas to 1900, *by Charles Singer. Pp. xviii*+525. *Clarendon Press, Oxford.* 1959. 35*s. net.*

Dr Singer's 'A Short History of Science' has long been one of the most widely used textbooks in the history of science. It had many weaknesses, however, which detracted from its value; names and dates, rather than the broad generalizations of science were emphasized, and it ended at precisely the point where science conquered the whole of the intellectual world.

'A Short History of Scientific Ideas to 1900' reflects Dr Singer's awareness of the inadequacies of the earlier volume. The factual basis remains firm, but a superstructure of general ideas has been added, thus giving continuity to the story of the development of science without which it remains lifeless. A new and lengthy chapter on science in the nineteenth century recounts the triumph of science as the earlier chapters recorded its struggles, thereby creating a dramatic unity lacking in the former work.

In a volume of such range, the specialist will inevitably find aspects with which he disagrees. The historian of medieval science might complain, with some justice, that the medieval achievement is dismissed rather too quickly. So, too, the historian of nineteenth-century science may feel that the allocation of space reflects the author's interests rather than historical reality.

There are many illustrations, not all of which aid in understanding the text. This is particularly true of the woodcuts, introduced no doubt to give a 'feel' for a period, but so blurred as to cause confusion.

A carefully compiled index and accurate printing enhance the value of the book to both students and teachers of the history of science.

L. PEARCE WILLIAMS

Short notices of books

(These notices are descriptive rather than critical and are designed to give a general indication of the nature and scope of the books.)

A Diderot Pictorial Encyclopaedia of Trades and Industry; Manufacturing and the Technical Arts in Plates Selected from '*L'Encyclopédie, ou Dictionnaire Raisonné des Sciences, des Arts et des Métiers*', *edited by Charles Coulston Gillispie. Vol. I, pp. xxx+208 plates; Vol. II, 277 plates. Dover Publications Inc., New York; Constable & Co., London.* 1959. 148*s. net.*

Diderot's great *Encyclopédie*, of which the first volume appeared in 1751, is too well known to need introduction. While the work was, and remains, a standard work of reference, its value today is limited by the fact that it is not readily accessible. The editor and publisher of the present work have therefore rendered an important service by reproducing—together with a brief commentary—485 of the handsome plates that are such a noteworthy feature of the original. The plates, mostly facsimile, have been selected mainly from those concerned with industry and crafts, ranging from agriculture to glass-making, from the textile industry to the making of artificial pearls.

The Physico-chemical Constants of Binary Systems in Concentrated Solutions, *Vol. I*, Two Organic Compounds, *by J. Timmermans. Pp. xiii+1259. Interscience Publishers Inc., New York; Interscience Publishers Ltd, London.* 1959. £10 18*s. net.*

Systems of two organic compounds, excluding hydroxyl derivatives, are dealt with in this book, which has collected the recorded physico-chemical data, under the general groupings of heterogeneous equilibria, properties of phases, and eternal constants for the mixtures. Full bibliographical data are also included.

The Sequestration of Metals, *by R. L. Smith. Pp. vii+256. Chapman and Hall Ltd, London.* 1959. 42*s. net.*

The graduate chemist to whom sequestering agents are, or could be, a useful tool, rather than a prime study, is the type of person for whom this book is intended. Sequestration is defined here as the suppression of a property or reaction of a metal, without either removal of that metal from the system or phase, or the concentration of the metal in any particular portion of the phase. The chemical and physical properties of the various sequestering agents are considered and later chapters deal with applications of sequestering agents to industry, to analytical chemistry, and to biology.

Nouveau traité de chimie minérale, *edited by P. Pascal. Vol. XI, pp. xxxix+850; Vol. XIV, pp. xxxix+1014. Masson et Cie, Paris. Vol. XI,* 1958; *Vol. XIV,* 1959. *Vol. XI: paper covers, fcs.* 7750; *bound, fcs.* 8950. *Vol. XIV: paper covers, fcs.* 9500; *bound, fcs.* 10 700.

Volume XI deals extensively with the chemistry of arsenic and its compounds, including forensic medical studies of the element. This section, which occupies more than half the volume, is written by R. Dolique and P. Pascal. The section on antimony is by P. Bothorel and that on bismuth by L. Domange.

The elements dealt with in volume XIV are chromium, in a section by J. Amiel, and molybdenum and tungsten. The latter are, in the main, discussed by J. Aubry and by A. Chrétien and W. Freundlich, respectively, but there is a section on the polyacids of these elements by L. Malaprude.

Structure Reports 1940–1950, *Vol. XIV, edited by A. J. C. Wilson. Pp. viii+215. International Union of Crystallography, Utrecht.* 1959. 68*s. net.*

This is a supplementary volume, containing only a few reports, but having cumulative indices for 1940–1950. The subjects are indexed by the names printed as the headings of reports, and some effort has been made towards including other common names; in the formula index, the constituents are arranged in the alphabetical order of chemical symbols.

Histo-chemical Technique, *by W. G. Bruce Casselman. Pp. 205. Methuen & Co. Ltd, London; John Wiley & Sons Inc., New York.* 1959. 18*s. net.*

The methods available for the chemical study of the structural components of cells and tissues as seen in microscopical preparations are described in this book. It discusses validity and errors in histochemistry and then gives descriptions of selected tests. The aim is always to emphasize the principles underlying the methods used.

An Introduction to Bacterial Physiology (*second edition*), *by E. L. Oginsky and W. W. Umbreit. Pp. xii+443. W. H. Freeman & Co, San Francisco; Bailey Bros. & Swinfen Ltd, London.* 1959. 64*s. net.*

The authors have aimed at bridging the gap between the undergraduate study of bacteriology and post-graduate work in bacterial physiology. The subjects covered include bacterial anatomy, populations, metabolism, and the capacity of the cell; the first edition was extensively revised to produce this one.

Anatomy of the Human Body, *by R. D. Lockhart, G. F. Hamilton and F. W. Fyfe. Pp. ix+697. Faber and Faber, London.* 1959. £5 5*s. net.*

The intention of the authors is to 'lighten the burden of the student of anatomy' by reduction of the number of words used in standard texts, by novel combinations of text and illustrations, and by the use of a large number of illustrations—there are over 950, many in colour. Emphasis has been laid throughout on function and on clinical application, so as to make the book useful to students of physiotherapy, radiography, and dentistry, as well as to medical students.

British Medical Bulletin, *Vol. XV, No.* 2, Blood Groups, *edited by K. L. G. Goldsmith. Pp.* 89–174. *The British Council, London.* 1959. 20*s. net.*

A. E. Mourant acted as the chairman of the committee that planned the symposia reported here, and he has also written the introduction. The book includes papers on the biochemistry of human blood group substances, on haemolytic diseases of the new-born, on the relation between blood groups and natural selection, on some associations between blood groups and disease, and on the significance of blood groups in terms of genetic linkage. It is intended to be of interest to the biochemist, the geneticist, and the biologist in general, as well as to those specializing in the field of blood groups.

Notes on contributors

J. F. RILEY,
M.B., Ch.B., M.D., Ph.D., D.M.R.T., F.R.C.S.E.,
Was born in 1912 in Settle, Yorkshire and was educated at Giggleswick School and Edinburgh University. He originally trained as a surgeon and, during the past war, commanded an Indian Mobile Surgical Unit in the Far East. His interest in cancer from the clinical point of view led him later to specialize in radiotherapy. He has written papers on various experimental aspects of the cancer problem and is especially interested in the mast-cell reaction that accompanies carcinogenesis in the skin of certain species.

A. C. CROMBIE,
B.A., Ph.D.,
Has been Senior Lecturer in the History of Science in the University of Oxford since 1953. He is a graduate in natural science of the Universities of Melbourne and of Cambridge, where he taught, and carried out research in, biology. In 1946 he became University Lecturer, and later Reader, of the History and Philosophy of Science in the University of London, and in 1953–54 he was Visiting Professor of Philosophy in the University of Washington, Seattle. During 1959–60 he will be Shreve Fellow at Princeton University. He is the author of two books, 'Augustine to Galileo. The History of Science A.D. 400–1650' and 'Robert Grosseteste and the Origins of Experimental Science 1100–1700', and of several scientific papers and papers on the history of science. He was the original editor of 'The British Journal for the Philosophy of Science'.

D. E. BLACKWELL,
Ph.D.,
Was born in London in 1921. Entered Cambridge University in 1940 and has remained there ever since, apart from three years during the war. He began research in 1946 on infra-red spectroscopy in the Department of Colloid Science, and in 1949 moved to the Solar Physics Observatory as Assistant Director. He participated in the 1952 eclipse expedition to Khartoum, observed the 1954 eclipse from an open high-altitude aircraft near the Faroe Islands, and attempted to observe the 1955 eclipse from a flying boat over the Pacific Ocean but was frustrated by cloud. He photographed solar granulation from a balloon at 18 000 feet in 1956, and in 1958 made an expedition to the Bolivian Andes to observe the zodiacal light.

J. P. DEWSBERY,
B.M., B.Ch., M.R.C.P., D.P.M.,
Was born in Sheffield in 1908 and educated at Ampleforth College, New College, Oxford, and the London Hospital, and qualified as a doctor in 1934. He was in the Royal Navy from 1940–45, with the Fleet Air Arm, in which he made a special study of psychological disorders occurring in flying personnel under wartime stress. Since early 1946 he has been on the medical staff of the Maudsley Hospital, where he is now a consultant.

W. T. STEARN,
Was born in Cambridge, England in 1911. He was librarian to the Royal Horticultural Society of London from 1932 to 1952, with the exception of four years in the R.A.F. He joined the botanical staff of the British Museum (Natural History), London in 1952. The flora of Jamaica is now his main field of research but he has written much on the nomenclature and taxonomy of cultivated plants, and on the bibliography and history of botany. He was secretary of the Stockholm and London committees which produced the 'International Code of Nomenclature for Cultivated Plants', and is the Linnean Society's Botanical Curator.

B. C. SAUNDERS,
M.A., Ph.D., Sc.D., D.Sc., F.R.I.C.,
Was an open scholar at Pembroke College, Cambridge. He later became a science master at Eton College, and then returned to Cambridge to work in the Department of Biochemistry. Subsequently he became Fellow and Praelector of Magdalene College, and University Lecturer in Organic Chemistry. Since 1939 his main fields of research have been (*a*) the synthesis and pharmacological examination of toxic organic compounds containing phosphorus and fluorine, (*b*) toxic organolead compounds, (*c*) peroxidase action. He has written numerous papers on these topics and is the author (and co-author) of five books. He is Senior Scientific Adviser in Civil Defence for the Eastern Region.

M. STACEY,
B.Sc., Ph.D., D.Sc., F.R.S., F.R.I.C.,
Born 1907 at Newport, Salop. Educated at Adams Grammar School, University of Birmingham, University of London, and Columbia University. Beit Fellow for medical research, London University (1933–7); reader in biological chemistry, Birmingham University (1943–6); professor of chemistry, University of Birmingham (1946–56); Mason Professor and Head of the Chemistry Department 1956–); Meldola medallist of the Royal Institute of Chemistry (1933); Tilden lecturer (The Chemical Society, 1946); winner (joint), 1950, of grand award of the sugar research foundation, National Academy of Science, New York; defence medal; vice-president of The Chemical Society; vice-president of the Midland branch of the Royal Institute of Chemistry; Chief Scientific Advisor to the Midlands for Civil Defence. Publications: over 200 scientific papers in the 'Journal of the Chemical Society,' 'Biochemical Journal,' etc. Member of the executive committee, 'Advances in Carbohydrate Chemistry'.

Some books received

(*Note.* Mention of a book on this page does not preclude subsequent review.)

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